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# The American Journal of Syphilis

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STUDY AND PREVENTION OF SYPHILIS

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## Original Articles

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### LATENT INFECTIONS WITH THE DEMONSTRATION OF SPIROCHETE PALLIDA IN LYMPHOID TISSUES OF THE RABBIT

BY WADE H. BROWN, M.D., AND LOUISE PEARCE, M.D.,  
NEW YORK, N. Y.

*From the Laboratories of The Rockefeller Institute for Medical Research*

(Received for publication, November 24, 1920.)

IN HUMAN syphilis there frequently comes a time during which the patient, although known to be infected, shows no obvious manifestation of an active syphilitic process. Within recent years, more exact clinical methods have shown that some of these patients are the subjects of visceral or of nervous involvement and are, therefore, cases of obscure rather than of latent infection. The work of Warthin<sup>1</sup> has shown further that active pathologic processes may exist where there are no clinical signs to indicate their presence and finally that spirochetes with more or less tissue alteration may be demonstrated in individuals where there was little if any evidence either of disease or of infection. The number of cases of latent syphilis, known and unknown, is probably a very considerable one and is of increasing importance to the syphilographer.



In rabbits, latency is a regular phenomenon of the infection. The primary lesions develop and heal spontaneously within a period varying from a few weeks to more than a year and if lesions occur elsewhere, they pursue the same course. Within a few months from the time of inoculation, therefore, no manifestations of infection may be found. This phenomenon has been spoken of as spontaneous recovery and is generally regarded as such since very few cases of relapse have been reported.

Relapses do occur, however, and while no estimation of their frequency can be given, they are more or less proportionate to the length and carefulness of the observation of infected animals. Spontaneous recovery in the rabbit is frequently only temporary and lesions of some kind may recur after the lapse of a few months and occasionally a year or more may intervene. During such intervals as these, the most careful examination fails to reveal the presence of a syphilitic lesion, either clinically or pathologically. These are cases of true latency or cases in which the animal, although still infected, has acquired some power of restraint upon the growth and multiplication of spirochetes and protection, for the time being, against their harmful effects.

If relapse occurs, we know that the animal was still infected but otherwise there is but one condition to indicate that infection may still exist and this is the presence of some degree of abnormality of the superficial lymph nodes, especially the popliteals. The changes noted in cases of latent infection vary from a shotty induration of small nodes to a moderate enlargement with some degree of induration.

This observation taken in connection with previous work on lymph node involvement during various stages of active infection<sup>2</sup> led us to undertake a small series of experiments which had two objects in view, namely, the demonstration of infection following so-called spontaneous recovery or during periods of latency, as the case might be, and the determination of the location of the spirochetes during such periods. The apparent abnormality of the popliteal nodes and the fact that in the active stages of infection, spirochetes were always demonstrable in these nodes by animal inoculation, suggested that the simplest method of approach to this problem was by excision of popliteal nodes and the inoculation of test animals according to methods described in a previous paper.\*<sup>2</sup>

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\*All operative procedures were carried out under ether anesthesia.



EXPERIMENTAL DEMONSTRATION OF SPIROCHETES IN THE  
POPLITEAL NODES

The experiments to be reported were carried out on six rabbits all of which had shown well marked generalized manifestations of disease but at the time the investigations were made, four of them showed no lesions of any kind while the other two showed slight lesions of an indifferent character in which no spirochetes could be demonstrated by dark-field examination. Three of the rabbits were infected with the Nichols strain of *Spirochete pallida* and three with the Zinsser-Hopkins strain.

For purposes of orientation, the essential points in the history of the six animals may be summarized as follows:

*Rabbit No. 1.*—Zinsser-Hopkins strain. Chancres of both scrota, recurrent chancres, and recurrent lesions of the skin and iris (slight).

Duration of infection, four years and three months; length of latent period, six months (?).

At the time of examination, there was a small area of thickening in the left scrotum the surface of which was covered with fine scales. No spirochetes could be demonstrated by dark-field examination. The popliteal nodes were slightly enlarged and indurated. The right node was resected for inoculation. The capsule and the node were slightly fibrous.

*Rabbit No. 2.*—Zinsser-Hopkins strain. Double orchitis with marked skin involvement followed by pronounced lesions of the bones and slight lesions of the skin and mucous membranes.

Duration of infection, nine months; length of latent period, three months.

At the time of examination, there were no demonstrable lesions present. The popliteal nodes were small but slightly shotty. The left node was removed for inoculation. The node was small and of a pale yellow color; the capsule was thick and opaque.

*Rabbit No. 3.*—Zinsser-Hopkins strain. Double orchitis followed by complete atrophy of both testicles; recurrent lesions in the testicles and scrota; pronounced involvement of bones, skin, cornea and iris with slight lesions of the mucous membranes.

Duration of the infection, seven months; length of latent period, three months.

At the time of examination, no lesions could be detected. The popliteals were moderately enlarged and indurated. The left node was removed. The capsule was thick and opaque and the node itself somewhat fibrous.

*Rabbit No. 4.*—Nichols strain. Double orchitis with marked skin involvement. Unusually marked affection of skin, bone, mucous membranes and eyes—a case of malignant syphilis.

Duration of infection, nine months; length of latent period, three months (?).

At the time of examination, there was a slight infiltration about the margins of the right nostril and there was some discharge from the nose. Examination

for spirochetes was negative. The popliteal nodes appeared to be slightly enlarged and indurated. The right node was resected for inoculation. The nodal mass was composed mostly of fibrous tissue; the parenchyma was small in amount.

*Rabbit No. 5.*—Nichols strain. Inoculated in the right testicle. Marked orchitis with skin involvement, metastatic lesion of the left testicle, marked cutaneous lesions and moderate infection of the bones.

Duration of infection, seven months; length of latent period, three months.

At the time of examination, no lesions were present. The popliteal nodes were moderately enlarged and indurated. The left node used for inoculation. The capsule was fibrous and thickened while the node itself was quite large, somewhat mottled and of a slightly yellow color.

*Rabbit No. 6.*—Nichols strain. Inoculated in the right scrotum. The scrotum and testicle were amputated forty-eight hours after inoculation. There followed a generalized disease with lesions of the left scrotum and testicle, marked bone lesions, and some lesions of the skin.

Duration of the infection, seven months; length of latent period, three months.

At the time of examination, no lesions were present. The popliteal nodes were distinctly enlarged and indurated. The right node was resected; its capsule was thickened while the node itself was enlarged and somewhat fibrous.

An emulsion was prepared from the popliteal nodes of each of these animals and 0.5 c.c. was injected into the right testicle of two normal rabbits. The results of the injections are shown in Table I.

TABLE I  
RESULTS OF INOCULATIONS FROM THE POPLITEAL NODES OF RABBITS DURING  
LATENT PERIODS OF INFECTION

SOURCE ANIMAL	DURATION OF INFECTION	LENGTH OF LATENT PERIOD	NUMBER OF TEST ANIMAL	RESULTS OF INOCULATION	INCUBATION IN DAYS
1*	51 months	6 months	1	+	38
			2	+	43
2	9 "	3 "	1	+	42
			2	+	44
3	7 "	3 "	1	+	37
			2	+	39
4*	9 "	3 "	1	+	34
			2	+	31
5	7 "	3 "	1	+	37
			2	Dead	
6	7 "	3 "	1	+	31
			2	+	31

+Indicates infection.

\*These two animals showed suggestive lesions at the time the examinations were made. They subsequently increased but no spirochetes could be demonstrated in them by dark-field examination.

The noteworthy features of these experiments are the constancy with which infection was demonstrated and the rapidity with which

infection developed in all of the test animals. In these respects, the results practically coincided with those previously obtained from the inoculation of lymph node material from cases of acute or active syphilitic infection. The incubation period was, in some instances, a few days longer, but averaged about the same in the two cases and was shorter than that usually obtained from blood inoculations except at the most active periods of infection. This was more than was to be expected.

It may be noted also that there was a degree of parallelism between the pathologic condition of the node and the length of the incubation period which was shorter in the case of nodes showing a medullary swelling than in those which were atrophic and fibrous.

Since the inoculations were made, four of the animals have shown no change from the condition recorded above and their period of latency has been extended by more than two months. In the case of Rabbit No. 1, the small area of infiltration in the scrotum increased in size until it formed an indurated nodule about 1 cm. in cross diameter and 0.5 cm. in thickness.

Rabbit No. 4 has also shown an increase in the lesions mentioned. Subsequent to the removal of the node for examination, there was an extension of the infiltration from the right nostril to the left and, while no examination has been made for spirochetes, the lesions which developed and are still present, present the typical appearance of syphilitic lesions in this locality.

The duration of infection or of the period of latency in the group of animals reported is not unusual except in Rabbit No. 1. The infection in this animal has at all times been a mild one; only a few lesions have developed and these have been comparatively slight. Nevertheless, virulent organisms have remained alive in the animal for approximately four years and a half. This is by far the longest case of animal infection on record and indicates very conclusively that the apparent recovery which takes place in these animals is only a symptomatic one.

#### DISCUSSION

These experiments are the first to show that rabbits which have recovered from the clinical manifestations of syphilis are still infected and that they may continue to harbor virulent spirochetes even though they show no clinical or pathologic evidence of infection except for the adenopathy described.



The continued existence of virulent organisms in these animals and the absence of lesions are very significant facts and indicate, as we believe, that some distinction may be drawn between immunologic processes which affect the growth and multiplication of the spirochetes and those which have to do with their localization and the development of lesions or the toxic effects of the organism.

Again, the constant recovery of spirochetes from the lymph nodes and the infectiousness of this material carry with them suggestions of possible seats of predilection for the spirochetes during latent periods of infection. Little is known of the ultimate location of the organisms during such phases of either the human or animal infection. The problem is difficult of approach from the human side and experiments thus far carried out on animals have not contributed to its solution.

During late stages of human syphilis, spirochetes have been demonstrated in a variety of tissues ranging from scars of the skin to the central nervous system—usually, however, in association with a definite syphilitic process. Likewise systematic examinations of the tissues of infected animals have been made by several investigators during periods of active infection using the method of animal inoculation. In this way, spirochetes have been recovered from a variety of sources, but the significance of the findings is rendered uncertain by the fact that at such times a septicemia exists which makes it impossible to differentiate between organisms in the blood passing through an organ and those localized in the tissues.

With the healing of the lesions, spirochetes disappear from the blood of the rabbit and numerous blood examinations made by us during latent periods of the infection (including one animal of the above group) have invariably given negative results. This source of confusion is, therefore, removed from the experiments which we have reported.

The work thus far done tends to show that a widespread distribution of spirochetes exists but it has not shown the points at which they come to rest during latent periods of infection. It is doubtful whether such points could be determined with absolute certainty by the means at our disposal, but the facts now known are sufficient to lend support to the assumption that the lymphoid tissues are the ones chiefly concerned.

Syphilographers have long recognized the existence of an affinity

of *Spirochete pallida* for lymphoid tissues and the adenopathy of syphilis is one of its most characteristic features. In like manner, it has been shown that, in all lesions, the points at which the spirochetes tend to accumulate in greatest numbers are the perivascular lymphatics.

These same conditions are equally true for the rabbit and during active periods of infection, spirochetes can always be recovered from superficial lymph nodes with greater ease and in greater number than from the blood; at times the nodes are almost as infectious as the active lesions. With the disappearance of lesions and of spirochetes from the blood, a condition develops in the rabbit which may be regarded as one of true latency. During this period, a slight adenopathy persists and spirochetes can still be recovered for months or even years from the most easily accessible masses of lymphoid tissue.

The assumption seems warranted, therefore, that while the spirochetes are widely distributed over the body during latent as well as active periods of infection, the distribution is not an indiscriminate one but that the chief reservoirs of infection are the lymphoid structures of the body whether massed as in the case of the lymph nodes or in the form of the simpler perivascular lymphatics. This points to the possibility of a wider application of our knowledge of lymphoid involvement in diagnostic and prognostic measures.

#### SUMMARY AND CONCLUSIONS

Six rabbits which had recovered from generalized syphilis were used as the basis for determining whether such animals were still infected and something as to the location of the spirochetes in cases of latent infection.

One of the animals was inoculated four years and three months prior to the examination, another nine months, and the others seven months. At the time the examinations were made, all of the animals showed a suggestive adenopathy which was most evident in the popliteal nodes. In addition, two of them showed slight lesions of an indifferent character in which no spirochetes could be demonstrated by dark-field examination. The others showed no lesions. The latent period of infection was of three months' duration in five of the animals and was six months in the other.

A popliteal node was removed from each of the animals and used for a test inoculation of two normal rabbits. Infection was produced

in all cases, the incubation period varying from 31 to 44 days which is practically the same as that given by lymph node inoculations during active stages of infection and shorter than that obtained from blood inoculations except in the most active stages of infections.

From these facts, it may be concluded that rabbits which have recovered from clinical manifestations of syphilis may harbor virulent spirochetes almost indefinitely even though no further manifestations of infection should occur. Moreover, the infectivity of material from the popliteal nodes, taken in conjunction with other evidence of an affinity of spirochetes for lymphoid tissues, is interpreted as indicating that the lymphoid tissues of the body in general are probably the chief reservoirs of the virus during latent periods of syphilitic infection. From this, it is suggested that a wider application may be made of our knowledge of lymphoid involvement in the management of cases of human infection.

#### REFERENCES

- <sup>1</sup>Warthin, A. S.: Amer. Jour. Med. Sci., 1916, clii, 508.  
<sup>2</sup>Brown and Pearce: Arch. Dermat. and Syph., 1920, ii, 470.



## STRAIN IN SPIROCHETES

BY BURTON PETER THOM, M.D., NEW YORK, N. Y.

*Visiting Syphilologist to the Hospitals of the Department of Correction,  
Blackwell's Island*

(Received for publication, July 20, 1920.)

THE question of strain in spirochetes has for some time attracted the attention of laboratory workers and clinicians. It is a most momentous one both from the standpoint of treatment and prognosis and is well worth profound study. It is my purpose here to give a brief survey of the problem as it now stands and to sum up the conclusions which I believe the facts warrant.

From time to time those engaged in the practice of medicine encounter that form of syphilis to which the adjective "malignant" is added to characterize its fulgurant and precocious symptoms which represent the comparatively benign course of the disease raised to the *nth* power as it were. Or it may be a peculiar perversity in relapses in spite of the most vigorous and intelligent treatment. Again, the involvement of the nervous system to the practical exclusion of the other tissue planes has caused many to assume that there are special strains of the infective organism having a definite selective predilection thereto. In the minds of many of those who have thoroughly studied the subject and who have had abundant opportunity to observe these phenomena the question is still in abeyance.

If, as it is asserted by some, malignant syphilis is due entirely to a *pars minoris resistentiæ*—to a lowering of tissue tone whereby the body cells are unable to overcome the invasion and therefore disintegrate with more rapidity than they otherwise would; the opponents of this theory will at once point to the case who previously to contracting the disease enjoyed perfect health and who was also an unusually robust and vigorous individual. The problem may be still further complicated by its being shown that the disease was contracted from one in whom the symptoms were very slight and had always been so.

The question of a particularly virulent strain of spirochetæ as the

cause of malignant syphilis is still an open one. Malignant syphilis, or galloping syphilis as it is called in England or *syphilis precosé* as it is called in France, has a certain peculiarity which is worthy of the closest attention. This peculiarity—and it is most peculiar—is that in many instances malignant syphilis registers a negative Wassermann reaction. I have personally observed it and I know that it has been observed and commented upon by others. Since this is so, it would seem to me to be somewhat far fetched to insist upon the severity of something the existence of which could not be demonstrated. Also the question of robustness and physical vigor is not always that of outward seeming. Resolved to finality it is always a question of the body cells—the minute particles, the ultimate units of which the body is composed and which in the last analysis determine the resistance of the organism as a whole. These, and not the body weight and degree of musculature determine the powers of resistance of the individual. This was noted long ago by Heitzman, who even affirmed that he could discriminate between cells of high and low resistance. The great clinician Nothnagel also observed that apparent vigor is not always combined with ability to resist disease.

The myth that malignant syphilis follows extragenital chancre has long been dispelled. But the opinion of the older writers, Fournier, Bassereau and others that malignant syphilis almost invariably followed phagedenic chancre and that the phagedenism was due to cachexia or inherent tissue weakness still stands the test of time. There is no reason to believe that malignant syphilis is due to any specially virulent strain of spirochetes.

The supporters of the belief of special strain in spirochetes find most of their evidence in syphilis of the nervous system. It must be admitted that much of this evidence is extremely difficult to controvert. "Facts are stubborn things"—they cannot be hidden or glossed over if an investigation is to be conducted in the true scientific spirit. The facts used to support the theory of spirochetal strain in nervous syphilis are of absorbing interest and I shall therefore discuss them in some detail.

The observations of Lambkin in the Uganda Protectorate in Africa and of various observers in China and Japan would indicate that syphilis among the black and yellow races in their original habitat is extremely rare. It would seem that when syphilis attacks a race in which it was hitherto unknown—a virgin soil as it were—as in



Uganda, the lesions are chiefly of the osseous and cutaneous systems. In China and Japan osseous syphilis is frequent but nervous syphilis is rare. It has therefore been held that the prevalence of nervous syphilis among the white civilized races and its infrequency among the darker and less civilized and savage races is due to (a) the difference of strains in the spirochetes, (b) the state of civilization—the lack of stress in the daily competition of life and in intellectual activity as compared with the mode of living among the civilized, (c) the degree of syphilization. Let us analyse these three propositions. First, that the rarity of nervous syphilis is due to a special strain of spirochete. From the days of Livingston to Col. Lambkin it has been known that syphilis only reached the black aborigines through contact with the whites. If nervous syphilis is common only to the white race, the spirochetal strains which produce it should breed true to form and produce a similar syphilis in the race to which it was brought. The second proposition that nervous syphilis is concomitant with the state of civilization is in my opinion much more reasonable. It is admitted by all that cerebral syphilis is much more frequent in brain workers than in those who earn their living by their hands. The symptoms of tabes are much more frequently observed in the legs, the organs of locomotion which are in constant use, than in the arms which are not used as much. The nervous system of the white race is more highly organized than that of the yellow or black races; it is therefore more vulnerable. By reason of the mode of living of the white race as a whole it is subjected to more stress. The corollary is simple. Increased vulnerability and stress render it more liable to attack. Again it is the *locus minoris resistentiæ*. The third proposition, that nervous syphilis is due to the degree of syphilization may in a measure be true. The syphilis of today is a much more attenuated syphilis than that of Ulrich von Hutten, or Paracelsus, or John of Vigo. In view of the fact that less than 5 per cent of all syphilitics ever develop nervous lesions, it may be taken as an evidence of the decreasing severity of the disease. But this does not seem to hold good among the Mongolians; because syphilis has been present among them fully as long if not longer than in the Caucasians and consequently there should be as much attenuation as represented by nervous syphilis, which we know there is not.

Nonne is of the opinion that neither paresis nor tabes are sequelæ

of syphilis; which means that he does not believe in the parasymphilis of Fournier or the metasymphilis of Möbius, but that these symptom-complexes are caused by the toxic action of the living spirochetes present and active in the nervous system. In other words, that they are simply forms of nervous syphilis *per se*. With him I fully agree. The question, "Is there a species of spirochetes which show a particular predilection for the nervous system?" is answered by him that there is at present no proof. He thinks it is reasonable to suppose, however, that there are strains of spirochetes which display a toxic effect upon the nervous system that is above the average.

Those who believe in a special strain of spirochete having a selective affinity for the nervous system are very prone to put forward conjugal syphilis, because of its undoubted frequency, in support of their theory. It must be admitted that on their face these examples are difficult to explain in any other way. But in this connection it must be remembered that the wives of syphilitic men are frequently—very frequently, I may say—infected without being aware of it. Under such circumstances they often go untreated, and it is well known as Fournier's statistics have shown that it is these untreated cases which most frequently develop tertiary lesions; and it is the tertiary type of nervous syphilis which we are in the main considering.

Drysdale has reviewed somewhat extensively the literature of conjugal neurosyphilis. He quotes many French authors and some German. All of these include reports in which the patients were infected by the same woman and all of whom later developed some form of neurosyphilis. Hereditary susceptibility can hardly be considered, neither can coincidence.

Ravine reports a woman brought into a clinic at Halle, Germany, in 1912. She was in a state of depression with the physical signs of paresis. Fifteen years before her husband was brought to the same clinic and his condition was diagnosed as paresis. He died of the disease in an asylum. Two years after the death of her first husband this woman married again and eight years later her second husband developed paresis and was sent to an asylum. He was still living when she was admitted. Permission was obtained to make a lumbar puncture on both husband and wife and with the cerebrospinal fluid thus obtained a characteristic keratitis was later produced in a rabbit.

Grossman had under observation a family consisting of a father,

mother and four children all of whom were affected with syphilis, the mother having acquired the disease from the father, the children by inheritance. All of them were affected with neurosyphilis. The father had a spastic hemiplegia, with unequal pupils that did not react to light and only sluggishly to accommodation. The mother had attacks of recurring headache accompanied with dizziness and nausea. Her pupils presented much the same phenomena as her husband's. Of the four children; the oldest had snuffles and an eruption at birth, was nervous and irritable, and generally below par mentally. Its pupils were widely dilated, unequal, and irregular, and failed to light accommodation, convergence, or to the instillation of physostigmin. The third child had an eruption at birth and convulsions at the age of seven years which were followed by spasticity of the legs. The pupillary changes were the same as in the oldest and in addition showed nystagmus, Babinski reflex, inexhaustible ankle clonus and increased knee and ankle jerks. The other two children gave a negative history in so far as eruptions or coryza were concerned, but their pupils were the same as the two oldest. From the evidence thus presented Grossman concluded that the spirochete causing this series must have had a selective action on the nervous system.

It is needless to go further with these clinical exhibits. They are interesting, but in my opinion they do not prove the existence of a special strain of spirochete with a selective action on the nervous system.

In support of the theory of special strains of spirochetes many observers claim to have noted variations in the morphology of the organism which might account for the character and predilection manifested by the lesions of the disease. Ten years ago, Noguchi, while carrying ten different series of spirochetæ through the testicles of rabbits for many generations was impressed by the fact that in some of the series the organisms were thicker or thinner than in others. Most of the series showed the usual thickness, length and undulations, but of these ten strains two were thicker ( $0.3\mu$ ) and one was thinner ( $0.2\mu$ ). The undulations of the thicker type were identical with the average, but those of the thinner were rather less pronounced and more closely set except at the extremities which were again quite typical. These characteristics were maintained unmodified throughout the numerous transfers from one rabbit to another for a period of over a year. Noguchi also noted that the thinner strain possessed greater



agility than the thicker strains. In so far as the production of the testicular lesions in the rabbits was concerned, the different series of spirochetes also showed different results. The seven series of typical morphology produced diffuse induration and tumefaction within three weeks, which continued for five or six weeks when spontaneous retrogression occurred. The two thicker series did not produce any changes in the inoculated testicles until five or six weeks had elapsed, when small, hard nodules developed. These nodules increased in size but always remained sharply demarcated from the surrounding tissue. They reached their maximum in from eight to ten weeks. These nodules were of cartilaginous hardness and contained a considerable amount of mucin. The thinner series which were obtained from a mucous patch of a patient suffering with malignant syphilis caused a diffuse testicular swelling in from ten days to two weeks which progressed rapidly for five or six days and then slowly retrogressed.

Noguchi later cultivated six series in which the organisms were taken directly from human syphilitic lesions, including chancres, condylomata and cutaneous papules. Of these, three showed the usual morphology, two were thinner and one was thicker. As a result of his researches Noguchi concludes that if a large number of cultures of the *Spirochete pallidum* are compared, whether taken from the testicular lesions artificially produced in a rabbit or from a human being, certain definite variations in their morphology will be apparent. These variations can be divided into thick, thin, and average specimens. The lesions as observed in the testicles of the rabbit also differed according to the strain with which they were inoculated, so that if this distinction were maintained in a very large number of series it is possible that it would throw some light on certain clinical features of the human disease. Noguchi is of the opinion that these morphologic and pathologic variations may constitute racial differences within the species.

Zinsser, Hopkins and McBurney kept alive five strains of spirochetes for from ten to more than twenty generations. Of these strains, four were obtained from human chancres and mucous patches. These observers noted that differences in virulence, period of incubation and the character of the lesions produced were not, in their opinion, characteristic of any special strain or the number of passages through rabbits they had undergone. The differences observed depended upon other factors which I shall enumerate.

1. When the spirochetes were obtained from recent diffuse lesions,

a higher degree of virulence and a shorter period of incubation was observed than when the organisms were obtained from older and more indurated lesions.

2. The highest percentage of successful inoculations and the shortest period of incubation were observed in rabbits with well-developed testicles.

3. The results produced were influenced largely by the technic of inoculation. When the tissue to be inoculated was thoroughly macerated and the inoculating material injected so as to thoroughly permeate the part, the period of incubation was decreased and the virulence of the injected material was increased. (This would mean that lessened tissue resistance causes increased virulence of the infective organism.)

4. The lesions were less marked the longer the interval between the removal of the inoculating material from one rabbit and its inoculation in another.

5. The character of the lesions were found to depend considerably upon whether they were developed in the substance of the testicle or in its sac.

In contradistinction to this Harrison states that the workers in the laboratory of the Army Medical School can breed at will strains which will produce a marked mucocutaneous efflorescence or those in which the cutaneous eruption will be comparatively slight, but showing a tendency to attack the nervous system. Pagniez in reviewing the recent work of Levaditi and others states that these workers can now produce a dermatropic and a neurotropic strain, and further, animals inoculated with one can develop a new primary lesion when inoculated with the other.

Nichols and Hough isolated a strain of spirochetes which showed a constant predilection to cause nervous lesions in rabbits. This strain was obtained from a patient who died from meningoencephalitis and its subsequent predilection for the nerve tissue of rabbits led Nichols to assume that this was an inherent characteristic of the strain. Reasoner also obtained a strain from a rapidly fatal case of nervous syphilis which caused early choroiditis in rabbits.

From the foregoing it would appear that able workers have arrived at opinions and results diametrically opposed. One or the other is wrong, or else the truth lies midway between these two extremes. We now know that the spirochetes are not the uniform

organisms they were first supposed to be. On the contrary, they are capable of many variations in morphologic character and clinical display. Dorflein has shown that there are undoubtedly different biological types of spirochetes. For example, intermittent fever in Europe, North America and East and West Africa has special clinical characteristics peculiar to these regions; yet it is caused by a spirochete that is morphologically identical in these, its widely separated habitats. But yet these seemingly different spirochetes may be distinguished by their different immunity reactions.

The spirochetel subdivision of the spirillum group to which the *Spirochete pallidum* belongs, comprises many others, most of which have been named and identified and are distinguished from each other by peculiarities of staining, size, number of spirals and other differences. Not infrequently, several forms occur in the same lesion or are found simultaneously in the same disease and they may thus exist side by side without the one exerting any influence upon the dyscrasia of which the other is the cause. The extreme tenuity of these organisms offers many difficulties in the way of discrimination, and errors of observation are extremely difficult to avoid. The statements of observers, even the most competent, must therefore always be received with a certain amount of reserve. In common with Hutchinson, I believe it possible that with advancing research we must be prepared to accept several variants of the spirochetel disease which we know as syphilis. It is possible—more—it is quite probable—that the parasite of syphilis may assume without by any means losing its identity, features as widely different as those which exist between the races of mankind or the different breeds of dogs. For that reason, it is not wise to impose limits to the possible variations of organisms of which, after all, our knowledge is far from complete. Even in the past there have been those who have suggested that there are really several maladies which resemble syphilis and which are usually classed as such clinically and which show the presence of the Wassermann reaction and of spirochetes. There are three which have retained this position, yaws, pian and goza. Castellani found in seven out of eleven cases of yaws a spirochete of extreme tenuity which morphologically was identical with the causative agent of syphilis. The observations of Castellani were later confirmed by Mayer and others. We now know the organism as being specific to yaws as the *Spirocheta pertenuis*. The identity of



yaws and lues has been denied by some competent observers and confirmed by others. All who have observed this disease cannot help but recognize the close clinical relationship which apparently exists between it and syphilis. This relationship is further enhanced by the fact that it responds like syphilis to the action of organic arsenic. As Hutchinson has said in regard to the two diseases, "If yaws be not syphilis, it is clear that it offers a very exact parallel to it."

It would seem to me, therefore, that if syphilis and yaws are not identical at the present time, it is more than possible that in the remote past an even closer relationship existed between them than exists now. I will even go so far as to say that I believe that the two disease entities have developed from a parent form, as it were, and that time and place have caused their present divergence. Because of this probable divergence in the past it is not, in my opinion, unreasonable to assume that the *Spirochete pallidum* may still continue to undergo changes in the way of increasing or diminishing its virulence or in its selective action in different individuals or under different conditions which we are not always able to identify. This would, I believe, go far in explaining the selective action of spirochetal "strains."

Every clinician knows that in syphilis as well as in all other diseases some individuals fail to respond to treatment even when skillfully carried out. The lesions persist in spite of the most painstaking and intelligent treatment. I have seen a gumma develop during a course of mercurial inunctions and ulcerative lesions of the buccal cavity appear within six weeks after an intensive course of salvarsan. We may well ask whether the failure to obtain results with drugs, which, with the exception of quinine and opium, are the most specific known to medicine, is due to "drug fastness" of the spirochete? For it has been asserted, and in my opinion with probability, that the organism of syphilis will develop an immunity to arsenic and mercury which renders these otherwise powerful therapeutic agents inert. Before the days of salvarsan the immunity which some syphilitics developed to mercury led Fournier to adopt the intermittent treatment, whereby the drug is given at intervals instead of continuously. Noguchi has shown in test tube experiments that the spirochete develops a tolerance to arsenic. McDonagh explains this failure of therapeutic effect to the different life cycles of the spirochete—one form of which is not susceptible to arsenic or

mercury. W. W. Graves, after a series of experiments with rabbits, also arrived at the same conclusion as McDonagh. I do not regard McDonagh's theory as proved by any means, but I am convinced from personal experience that the organisms frequently become arsenic and mercury fast, as it were, and in consequence these drugs sometimes fail in their usual effect.

After thus reviewing the subject it seems to me I am justified in arriving at the following conclusions; none of which, I may say, are final; for there is no telling what further research may bring forth. Without wishing to appear dogmatic I would say:

Malignant syphilis is not due to excessive virulence of the infecting agent. It is entirely a question of individual idiosyncrasy, due to causes in some instances which at present we do not understand. These causes are probably cachexia and an inherently low tissue resistance although such an individual may seemingly possess robust health.

Nervous syphilis, including the so-called conjugal neurosyphilis, offers the best evidence that we have of the selective action of a special strain of spirochete. But with all the evidence thus far presented, it does not in my opinion go far enough to prove absolutely the existence of such strains. The well known aberrancy of the disease and the not to be omitted fact of individual idiosyncrasy are unsurmountable obstacles in the way of its complete acceptance. While admitting the facts, I personally believe that the last mentioned is the one most to be considered in the development of nervous lues.

It is undoubtedly true that some observers have noted decided variations in the morphology of the organism for which no explanation can be given. But it by no means follows that these morphological variations will produce variations in the pathologic expression of the disease.

It has been proved conclusively that in experimental syphilis at least, differences in virulence, in the period of incubation and in the character of the lesions can arise through differences in technic without the question of strain entering into the calculations at all.

Hutchinson's suggestion that there may be several variants of syphilis is plausible, but it is not capable of proof—at least, not yet.

The possibility of the *Spirochete pallidum* having a life cycle which accounts for the pathologic preferences sometimes displayed by the



disease has been advanced. This I am not prepared to accept although advocated by respectable authority. It is possible, but, in my opinion, hardly probable.

On the whole I am convinced that there is no such thing as "strain" in spirochete. Individual idiosyncrasy, if properly investigated, will account for all of the seeming vagaries of the disease. In other words the selective action of the *Spirochete pallidum* when introduced into the body is governed entirely by the manner in which the tissues of the host react to the invader.

## SYPHILIS AS AN ETIOLOGIC FACTOR IN NODULAR CIRRHOSIS OF THE LIVER

BY L. J. OWEN, M.D., ST. LOUIS, MO.

*From the Department of Pathology of Washington University School of Medicine*

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THE belief that chronic infection is an etiologic factor in the production of liver cirrhosis has been supported by bacterial observations and experiments on animals. Adami<sup>1</sup> has discussed this evidence and has maintained that the colon bacillus has a part in the production of cirrhosis. Fox<sup>2</sup> has reviewed records of 3,200 autopsies on animals of the Philadelphia Zoological Gardens and collected seventeen cases of liver cirrhosis. He points out that factors such as alcohol, lead and syphilis can have no part in the production of these lesions and emphasizes the importance of infection though he fails to define the nature of the infections which are responsible for the disease.

It has been shown that the liver cells and endothelial cells of liver are phagocytic in action towards bacteria, and thus the liver probably receives more bacteria, the spleen possibly excepted, from acute and chronic infection in the body than any other tissue. This is especially true in peritoneal infections. Bartlet and Ozaki<sup>3</sup> working with dogs infected with *Micrococcus aureus* have demonstrated this accumulation of bacteria in the liver. Berry and Milich<sup>4</sup> have shown this relation by intraperitoneal injection of infectious material into pigeons. Welch and Blackstein<sup>5</sup> have shown that colon bacilli and typhoid bacilli injected into the blood stream of rabbits appear in the bile.

Grover<sup>6</sup> in 1913 briefly reviewed the literature on experimental production of liver cirrhosis, and published a report on work of his own. He infected rabbits with *Staphylococcus aureus* and the colon bacillus. His conclusions are that repeated injury of the liver cells results in their ultimate destruction and replacement by scar tissue. Hektoen<sup>7</sup> used a bacillus of the colon group and one belonging to the pseudodiphtheria group and succeeded in producing well-marked perilobular cirrhosis of the liver in guinea pigs. Ogata<sup>8</sup> obtained

some proliferation of connective tissue in the interlobular spaces by repeated injection of killed colon bacilli into the portal and mesenteric veins; but the changes were not the same as those of Laennec's cirrhosis.

The possibility that a combination of intoxication and injection might produce cirrhosis was suggested by Opie.<sup>10</sup> He used combined infection with colon bacillus and intoxication by chloroform, and produced advanced cirrhosis; whereas use of these same agents separately produced the same inconstant and uncertain results obtained by most of those who have studied this problem.

The present discussion deals with the type of cirrhosis which has been known variously as Laennec's, atrophic, nodular, and alcoholic cirrhosis.

Syphilis as an etiologic agent in the production of nodular cirrhosis has been denied by some and affirmed by others. Symmers<sup>11</sup> has published some very interesting data regarding the association of syphilis with this condition. He finds the Wassermann reaction positive in 80 per cent of cases of atrophic cirrhosis in the wards of Bellevue Hospital. Of instances of cirrhosis confirmed at autopsy, 28 per cent were in syphilitic subjects. This cirrhosis with syphilis could not be differentiated from that in nonsyphilitic subjects, or at least where no syphilis was found.

Woolley<sup>12</sup> reports 3 cases of cirrhosis, in 2 of which syphilis was demonstrated, and believed that syphilis was present though not proved in the third.

McNeil<sup>13</sup> reports 64 cases clinically diagnosed cirrhosis in 1200 syphilitics. In another series of 1000 autopsies, 9 per cent were shown to have cirrhosis of the liver, and in this series 30 per cent of those who were syphilitic had cirrhosis. In these the type commonly known as "syphilitic" cirrhosis, characterized by broad deforming scarlike bands of fibrous tissue was not common, the lesion being nodular, or so-called atrophic cirrhosis. Alcohol does not seem to have been an important etiologic factor in this series of cases.

To obtain data for the following report 1200 autopsies performed in the pathologic laboratory of Washington University School of Medicine were reviewed. It was found that 8.5 per cent of all adults had cirrhosis of the liver, and of these 80 per cent were of the nodular type. All other types of cirrhosis have been omitted. There were in the present series three instances of typical syphilitic cirrhosis, characterized by deforming bands of scar tissue. (Autopsies 44,



71, and 239); one instance of obstructive cirrhosis with suppurative cholangitis caused by calculi lodged in the common duct (Autopsy 1009); and one instance of primary carcinoma of the liver with cirrhosis (Autopsy 1137). The clinical histories were studied and a table has been made showing factors which might have had a part in bringing about the liver condition. Associated lesions possibly resulting from the same causes as cirrhosis are enumerated.

The following is a brief summary of the clinical and anatomic findings in these cases:

CASE 1.—Autopsy No. 86. Male; aged forty-five years. Past history negative except for alcoholism (8 drinks of whisky and 20 drinks of beer daily). Patient entered the hospital with an acute abscess of the chest wall following trauma. Wassermann reaction was positive and a diagnosis of syphilis was made.

*Anatomic Diagnosis.*—Granulating wound of chest wall; hemorrhages of all mucous membranes; acute pyelitis; pyelonephritis; acute splenic tumor; fatty degeneration of viscera; chronic aortic endocarditis; nodular (Laennec's) cirrhosis of liver; ascites; arteriosclerosis.

The liver weighed 2400 grams; the surface was rough, nodular, and the capsule very much thickened. There was considerable resistance to the knife on section. The cut surface revealed a diffuse fibrosis throughout the liver. Microscopically the liver tissue is separated into islands by encircling bands of fibrous tissue.

CASE 2.—Autopsy No. 168. Male; aged sixty-eight years. The patient has had malaria; he has drunk beer in considerable quantity; early death of four children from cause unknown has occurred. No Wassermann reaction was performed. The clinical diagnosis was, acute general peritonitis, cirrhosis of liver, ascites, chronic nephritis. The saphenous vein was transplanted into the peritoneal cavity.

*Anatomic Diagnosis.*—Cirrhosis of liver; ascites; acute peritonitis; double hydrocele; brown atrophy of heart; chronic nephritis; pancreatitis; atheroma of aorta; perisplenitis; emphysema.

The liver weighed 1030 grams; the surface was roughened and nodular; the capsule was not thickened appreciably; on section there was definite resistance to the knife. Microscopic study of the liver showed broad bands of fibrous tissue separating parenchyma into islands.

CASE 3.—Autopsy No. 329. Female; aged twenty-seven years. Patient was admitted to the hospital in a comatose condition; and a diagnosis of tuberculous meningitis was made and confirmed. The Wassermann reaction was negative.

*Anatomic Diagnosis.*—Tuberculous meningitis; pleuritis; peritonitis; solitary tubercle of brain; pulmonary tuberculosis; acute nephritis; cirrhosis of liver; chronic salpingitis; chronic adhesive peritonitis; mucous luteum.

The liver weighed 1195 grams; there were a few nodules on the surface, and there was some resistance to the knife on sectioning. The lobules were distinct on cut section. Microscopic study of liver showed thin strands of connective tissue in the portal spaces, and there were a few islands of isolated parenchyma. There were some areas of focal necrosis.

CASE 4.—Autopsy No. 377. Female; aged forty years. Patient was admitted to hospital with an acute streptococcus pharyngitis, fatal septicemia developing shortly after admission. The patient had had intercommunicating fistulæ of rectum, vagina and bladder for a period of several years. No Wassermann reaction was performed. There was no history of alcoholism.

*Anatomic Diagnosis.*—Fecal, rectovaginal and rectovesical fistulæ; ulcerative cystitis; vaginitis; brown atrophy of heart; fatty cirrhosis of the liver; chronic interstitial nephritis; amyloid degeneration of liver; kidneys, and spleen.

The liver weighed 1580 grams; the capsule was thickened; the cut surface showed an increase in fibrous tissue, and was very fatty. Microscopic study showed a definite increase in perilobular connective tissue, and the presence of extensive fatty degeneration.

CASE 5.—Autopsy No. 423. Male; aged sixty-one years. The patient was admitted to the hospital suffering from an esophageal cancer. There was complete obstruction to the passage of food, and a gastrostomy was done. No Wassermann reaction was performed, and there was no history of alcoholism or infection.

*Anatomic Diagnosis.*—Squamous cell cancer of the esophagus; chronic nephritis; cirrhosis of liver; arteriosclerosis.

The liver weighed 1580 grams and had a very fatty appearance; the capsule was definitely thickened, and the cut surface showed an increase of connective tissue in the portal spaces. Microscopic study showed a definite increase in connective tissue most evident in portal spaces, and there was a slight round cell infiltration.

CASE 6.—Autopsy No. 509. Female; aged seventy-four years. Patient was admitted to the hospital with complaint of swelling of the legs and abdomen. The past history was negative except that patient had had an attack of jaundice when young. No Wassermann reaction was performed. Clinical diagnosis; atrophic cirrhosis of liver, chronic local peritonitis, chronic nephritis, cardiac hypertrophy and anemia.

*Anatomic Diagnosis.*—Atrophic cirrhosis of the liver; peritonitis with ascites; arterial sclerosis; chronic nephritis; cardiac hypertrophy; chronic splenitis; pyelitis; cystitis; endometritis; cholecystitis; cholelithiasis; emaciation.

The liver weighed 1350 grams. The surface was rough and nodular and the capsule was not thickened. On cutting there was resistance to the knife, and the cut surface presented irregular mottling, with elevated areas which were from 5 mm. to 15 mm. in diameter. Microscopic study showed fine bands of fibrous tissue encircling islands of parenchyma. There was necrosis of the parenchyma where fibrosis was most dense.

A smear from fluid in the pelvis contained no microorganisms, and a culture from the blood of the heart remained sterile.

CASE 7.—Autopsy No. 577. Male; aged fifty-five years. Patient had been admitted to the hospital six times in the four months previous to death, and had the Thalma operation performed on him. The Wassermann reaction was negative, and there was no history of alcoholism. Clinical diagnosis: atrophic cirrhosis of liver, aortic and mitral valve disease, arteriosclerosis.



*Anatomic Diagnosis.*—Laennec's cirrhosis; edema and congestion of intestines; chronic nephritis; chronic fibrous myocarditis; acute vegetative endocarditis; chronic pancreatitis; healed pulmonary tuberculosis.

The liver weighed 1400 grams. The surface was nodular, the nodules averaging 3 mm. in diameter. On cutting there was resistance to the knife and the cut surface showed mottling of reddish gray areas and gray lines. Microscopic study showed a diffuse formation of fibrous tissue dividing and compressing parenchyma into islands. There was present considerable atrophy of parenchymal cells.

CASE 8.—Autopsy No. 579. Male; aged fifty-two years. Patient admitted to hospital suffering with chronic infectious arthritis. His mother had died of "liver cirrhosis." Patient had been a constant user of beer. Wassermann reaction was negative. Clinical diagnosis; chronic aortic and mitral valve disease, cardiac dilatation, chronic infectious arthritis.

*Anatomic Diagnosis.*—Aortic and mitral stenosis; cardiac hypertrophy; arterial sclerosis; infarcts of lung; cirrhosis of liver; pericardial and pleural effusion; ascites.

The liver weighed 1330 grams. The surface was slightly granular, dark brown, and the capsule opaque. The cut surface was dark with a deeper color in the centers of the lobules. Microscopic study showed a diffuse fibrosis of the interlobular spaces of the liver, the connective tissue increase in places was intra-lobular. There was some atrophy of parenchymal tissue.

CASE 9.—Autopsy No. 652. Male; aged fifty-two years. The patient was admitted to the hospital with abdominal and pleural effusion. The patient had a chancre which was followed by vigorous treatment for syphilis. He had been a moderate user of beer all of life. Wassermann reaction was reported negative. Clinical diagnosis: tuberculosis of pleura, peritoneum and lungs; multiple abscesses of kidneys; atrophic cirrhosis of liver; mitral valve disease.

*Anatomic Diagnosis.*—Tuberculosis of lungs, pleura and peritoneum; atrophic cirrhosis of liver; chronic mitral endocarditis.

The weight of liver was 1700 grams. The surface was nodular, and on section the peripheries of the lobules showed as depressed lines. Microscopic study showed the diffuse fibrous bands separating the liver tissue, characteristic of this type of cirrhosis. There is present atrophy and fatty degeneration of parenchyma.

Cultures from the blood of the heart contained *Streptococcus pyogenes* and *Staphylococcus aureus*; cultures from the liver remained sterile.

CASE 10.—Autopsy No. 709. Male; aged sixty-two years. Patient was admitted to hospital suffering from an acute alcoholic psychosis. There was a history of having had a chancre, and of abuse of alcohol for many years. The patient had received antiluetic treatment and Wassermann reaction was negative. Clinical diagnosis: alcoholic psychosis; atrophic cirrhosis; chronic nephritis.

*Anatomic Diagnosis.*—Aortic stenosis; arterial sclerosis; nephritis; mitral endocarditis; infarcts of lung, spleen, and kidneys; atrophic cirrhosis of liver.

The liver weighed 980 grams. It was firm, yellowish brown, and had a warty appearance. The cut surface displayed a nodular bulging on section and was bile stained. Microscopic study showed fibrous bands scattered diffusely through

liver, but the fibrosis was not very dense. There was some degeneration of liver cells and fatty changes present.

Culture from the blood of the heart and from the spleen, kidney and liver remained sterile.

CASE 11.—Autopsy No. 711. Male; aged thirty-five years. Patient was admitted to the hospital with a swelling in the neck which proved to be Hodgkin's disease. The patient had been an occasional user of beer; and there was a history of attacks of sore throat. No Wasserman reaction was performed.

*Anatomic Diagnosis.*—Hodgkin's disease; chronic nephritis; portal cirrhosis; arterial sclerosis; pleural effusion; fibroid nodules in kidney.

The liver weighed 1625 grams, was firm, yellowish brown in color, and surface showed nodular elevations 1 to 2 mm. in diameter. The cut surface showed a similar nodular bulging. Microscopic section of liver showed rather broad bands of connective tissue scattered diffusely through liver, and dividing parenchyma into islands of tissue.

Cultures from the blood of the heart and from the liver remained sterile.

CASE 12.—Autopsy No. 752. Male; aged eighty years. Patient was admitted to hospital with symptoms referable to cardiac valvular disease and cirrhosis of liver. Patient had used alcohol excessively for ten years at a previous period of life from about 40 to 50 years of age). No Wassermann reaction was performed.

*Anatomic Diagnosis.*—Laennec's cirrhosis; ascites; arterial sclerosis; coronary sclerosis; chronic nephritis; myocarditis; mitral and aortic endocarditis; edema of lungs; chronic pancreatitis; scoliosis; perisplenitis.

The liver weighed 1020 grams; the surface was nodular, very firm, and on section there was resistance to the knife. The cut surface displayed lobules marked out by gray depressed lines. Microscopic section showed very extensive parenchymal atrophy and formation of diffuse bands of fibrous tissue.

Cultures from the blood of the heart and from the liver remained sterile.

CASE 13.—Autopsy No. 776. Female; aged forty-seven years. Patient was admitted to hospital with an acute abdominal condition. There was a history of several stillbirths and early death of several children. The patient had used beer steadily for many years. Wassermann reaction was positive and epilepsy was present.

*Anatomic Diagnosis.*—Arterial sclerosis; hemorrhage into cerebellum; edema of lungs; cholelithiasis; cholecystitis; chronic endocervicitis; chronic pelvic peritonitis; chronic nephritis; mitral endocarditis; cirrhosis of liver.

The liver weighed 1695 grams; the capsule was thickened. The cut surface showed projecting nodules marked out by thin gray bands. Microscopic study showed the presence of thin bands of fibrous tissue in interlobular spaces.

Cultures from the heart's blood and liver remained sterile; cultures from the gall bladder contained *Streptococcus viridans* and *B. coli*.

CASE 14.—Autopsy No. 801. Male; aged forty-nine years. Patient was admitted to hospital with symptoms referable to nephritis and cirrhosis of liver. There was a history of chancre; and of excessive use of whisky over a long period of time. The Wassermann reaction was positive.

*Anatomic Diagnosis.*—Laennec's cirrhosis; icterus; ascites; chronic nephritis; luetic aortitis; endocarditis; pleurisy; scars in omentum.



The liver weighed 970 grams; it had a hob-nailed appearance, and its capsule was thickened. On section there was resistance to the knife, and the cut surface showed lobular elevations which were surrounded by fine gray bands. Microscopic study of liver revealed extensive cirrhosis; the fibrous bands were broad and diffusely scattered through whole tissue.

Cultures from the blood of the heart, from the liver and from the kidney remained sterile.

CASE 15.—Autopsy No. 803. Male; aged forty-eight years. Patient was admitted to the hospital with ascites, gastric disturbance, and symptoms referable to nephritis. There was a history of chancre, gonorrhea, and moderate use of alcohol.

*Anatomic Diagnosis.*—Atrophic cirrhosis; icterus; ascites; chronic catarrhal gastritis; chronic interstitial pancreatitis; edema of legs; aortic endocarditis; myocardial scar; arterial sclerosis; chronic nephritis with granular kidney; chronic cystitis; chronic prostatitis; plueral adhesions.

The liver weighed 1035 grams; it was very firm, light brown in color, and the surface was nodular. On section there were rounded projecting areas surrounded by thin depressed gray bands of tissue. Microscopic section showed marked proliferation of fibrous tissue forming broad bands, dividing liver tissue into islands.

Cultures from the heart's blood, liver, spleen and kidneys remained sterile. Spirochetes were not found in sections of the liver prepared by Levaditi's method.

CASE 16.—Autopsy No. 913. Male; aged twenty-eight years. Patient was admitted to the hospital complaining of cardiac distress. The patient had used alcohol in large quantities for many years (saloon keeper); and there was a history of syphilis and gonorrhea. The Wassermann reaction was positive.

*Anatomic Diagnosis.*—Atrophic cirrhosis; ascites; icterus; chronic nephritis; arterial sclerosis; cardiac dilatation; cholecystitis cholelithiasis; perisplenitis; fatty liver; acute splenic tumor.

The liver weighed 1220 grams; the surface was rough and nodular, and nodules appeared to be surrounded by thin fibrous bands. On section there was definite resistance to the knife, and the gray bands surrounding nodules of liver tissue were distinct. Microscopic section showed very fine bands of fibrous tissue widely scattered through parenchyma. Culture from the heart's blood and liver remained sterile.

CASE 17.—Autopsy 997. Male; aged sixty-one years. Patient was admitted from the out-patient department with a diagnosis of heart block. The patient was a cigar maker but denies excessive use of tobacco. There is a history of gonorrhea; and Wassermann reaction is negative.

*Anatomic Diagnosis.*—Arterial sclerosis; chronic mitral endocarditis; myocarditis involving bundle of His; cardiac hypertrophy and dilatation; chronic nephritis; cirrhosis of liver; perisplenitis; cholecystitis; cholelithiasis; chronic peritonitis.

The liver weighed 1520 grams; the surface was finely nodular. The cut surface was deep red, with lobular areas distinct and separated by grayish bands. Microscopically the cirrhotic bands were not very dense with fibrous tissue tending to penetrate lobules and become intercellular.



CASE 18.—Autopsy 1069. Male; aged forty-two years. Patient was admitted suffering from an acute abdominal condition, and died on the following day. Clinical diagnosis was general peritonitis.

*Anatomic Diagnosis.*—Acute diverticulitis of Meckel's diverticulum; acute splenic tumor; arterial sclerosis; dilatation and hypertrophy of heart; healed pulmonary tuberculosis; cloudy swelling of the viscera; cirrhosis of liver.

The liver weighed 2890 grams; the surface was uneven and slightly hob-nailed. On cutting there was resistance to the knife, and depressed lines of grayish fibrous tissue were seen. Microscopic study showed areas of fibrous tissue increase, leaving some spaces free. There was some fatty change present in the parenchyma.

Cultures from the blood of the heart contained *Streptococcus hemolyticus* and *B. coli*.

CASE 19.—Autopsy 1084. Female; aged forty years. Patient was admitted to the hospital in an eclamptic condition following a forceps delivery. There had been one to two miscarriages per year for the past twelve years, and the patient had had one operation for ectopic pregnancy. No Wassermann reaction was performed.

*Anatomic Diagnosis.*—Postpartum uterus; acute and chronic nephritis; acute splenic tumor; cloudy swelling of the viscera; cirrhosis of the liver; chronic peritonitis; fibrous calcified nodules in lung, liver and spleen.

The liver weighed 1175 grams; the capsule was thickened and bile stained. On cut surface the lobule-like areas are distinct, and periportal spaces seem thickened. Microscopic study showed fibrous tissue increase in perilobular spaces, with central necrosis in many lobules.

Cultures from the blood of the heart remained sterile.

A study of percentages in the accompanying table reveals a high incidence of syphilis; excessive use of alcohol, and a combination of the two. Of the Wassermann tests with nodular cirrhosis 42 per cent were positive. In two other cases (Cases 9 and 10) though the Wassermann was negative, lues could be diagnosed by clinical evidence; these cases bring the incidence of positive syphilis to 58 per cent among the instances in which syphilis was adequately searched for. If the cases in which no Wassermann test was made are included, the percentage of syphilis still reaches 37 per cent of the total. There are two other cases in which syphilis was possible. In one the early unexplained death of four children occurred; and in the other there was a history of 12 or more miscarriages.

The incidence of alcoholism is less than that of syphilis, a history of alcoholism being obtained in 37 per cent of cases where inquiry was recorded and only 26 per cent of the whole.

The combination of syphilis and alcohol is high, and is of great interest from the viewpoint of combined etiology investigated by

## NODULAR CIRRHOSIS OF LIVER

CASE	SEX	AGE	WASSERMANN *	ALCOHOLISM	EVIDENCE OF SYPHILIS	ENDOCARDITIS†	MYOCARDITIS	NEPHRITIS	ARTERIOSCLEROSIS	FATTY DEGENERATION	ASCITES	CHRONIC PERITONEAL INFECTION	PERISPLENITIS	CHOLECYSTITIS	CHRONIC INFECTIOUS ARTHRITIS	PANCREATITIS	ICTERUS
1	M	45	+	+	Aortitis	A	+	+	+	+							
2	M	68	0	-	Early death of 4 children		+	+	+		+		+			+	
3	F	27	-	-				+				+					
4	F	40	0	-			+	+		+		+					
5	M	61	0	0				+	+								
6	F	74	-	-				+	+		+		+	+			
7	M	55	-	-		A M	+	+			+					+	
8	M	52	-	-		A M			+		+				+		
9	M	52	-	-	Chancre	M		+			+						
10	M	62	-	+	Chancre	A		+	+		+						
11	M	35	0	-				+	+								
12	M	80	0	+		A M	+	+	+	+	+		+		+		
13	F	47	+	+	Stillbirths	M		+	+		+	+	+	+			
14	M	49	+	+	Chancre aortitis	A		+			+						+
15	M	48	+	-	Chancre	A	+	+	+		+						+
16	M	58	+	+				+	+	+	+		+	+			+
17	M	61	-	0		M	+	+	+					+			
18	M	42	0	0					+								
19	F	40	0	0	12-15 miscarriages			+									

\* + Positive Wassermann. - Negative Wassermann. 0 Absence of Wassermann.

† Aortic endocarditis. M. Mitral endocarditis.

Dr. Opie. This combination occurred in Cases 1, 10, 14, and 16 (and perhaps in Case 13, recorded in the table as negative). Of the cases positively syphilitic, over half had used alcohol excessively over a long period of time.

The percentage of men is higher than that of women, being 74 per

cent for men and 26 per cent for women. The higher incidence of cirrhosis of the liver in men is perhaps explained by the greater frequency of alcoholism in men.

Chronic infections other than syphilis are perhaps important factors in the production of liver cirrhosis. There were two cases, Cases 8 and 12, which were diagnosed clinically as chronic infectious arthritis. Syphilis was not demonstrated in either of these cases, but alcoholism was present in one (Case 12); and perhaps doubtful in the second (Case 8) recorded in the table as negative.

Endocarditis occurred in ten instances or 52.5 per cent of all cases. These have been classified in the table as aortic and mitral valvular disease. There were seven instances of disease of the aortic valve, Cases 1, 7, 8, 10, 12, 14 and 15; two of which were definitely syphilitic in origin, namely, Cases 1 and 14; and two others associated with syphilis and probably due to that infection. Of six instances of mitral valve disease, Cases 7, 8, 9, 12, 13 and 17, only one was associated with aortic valve and mitral valve disease were coexistent in three cases, in none of which was there evidence of syphilis.

#### CONCLUSIONS

The frequent association of syphilis with nodular (Laennec's) cirrhosis of the liver (present in 40 per cent of 19 instances of nodular cirrhosis) indicates that it is an etiologic factor in the production of the hepatic lesion.

The occurrence of alcoholism in association with syphilis indicates that a combination of the two factors may produce the lesion.

Other chronic infectious processes, such as chronic arthritis and endocarditis have been associated with cirrhosis with sufficient frequency to warrant the collection of further data concerning their relation to cirrhosis.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XV\*

### THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE ANTICOMPLEMENTARY ACTIVITY OF ORGAN EXTRACTS (ANTIGENS) AND SERA

BY JOHN A. KOLMER, M.D., AND MARY E. TRIST, PHILADELPHIA, PA.

*From the Dermatological Research Laboratories of Philadelphia*

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AS is well known the organ extracts employed as antigens in the syphilis complement-fixation reaction may absorb or fix a slight amount of complement or actually cause the inactivation of a portion, these effects being designed as the anticomplementary activity of antigen. To avoid nonspecific complement-fixation reactions due to these factors, the antigens are titrated and employed in amounts much less than found to exert these anticomplementary effects but even these amounts are known to absorb or fix some complement, which is overcome in practice by using an excess of complement or hemolysin.

Likewise human sera frequently contain substances causing a similar nonspecific fixation or inactivation of complement which are usually removable by heating at 55° C. for fifteen minutes (1), although they may be thermostable and resist heating for longer periods of time. Curiously, the serum of a healthy nonsyphilitic person may contain such slight amounts of these anticomplementary substances as to yield a satisfactory serum control of complete hemolysis and yet in the presence of an antigen show incomplete hemolysis, due to the summation of the so-called anticomplementary effects of serum and antigen, which separately were without demonstrable anticomplementary activity in the controls of the test.

#### PURPOSES OF INVESTIGATION

Ordinarily complement is titrated by mixing the complement serum, hemolysin and corpuscles at once and incubating at 38° C. for

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

one hour; as shown in a previous article (2) some destruction of complement inevitably occurs during a primary incubation which is particularly marked when the complement is titrated in the presence of antigen with a primary incubation of four to eighteen hours at 8° C. to 10° C. with or without an additional incubation at 38° C. For this reason it is important to *study the influence of temperature and duration of primary incubation upon nonspecific complement fixation or anticomplementary activity by antigen alone and serum alone*, which constitute the purposes of this investigation in relation to studies bearing upon the primary incubation for complement-fixation tests.

### Part 1

#### THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE ANTICOMPLEMENTARY ACTIVITY OF ANTIGENS

*Technic.*—In conducting these experiments guinea pig complement was titrated plain and without primary incubation by mixing varying amounts of serum with constant amounts of antisheep hemolysin and corpuscles and water-bath incubation of one hour when the unit was read.

Each organ extract was diluted 1:10 with physiologic saline solution and used in amounts of 0.1 to 1 c.c. with two units of complement; with each antigen and complement at least 17 sets were prepared, each set being given a different period of primary incubation before the addition of one unit of hemolysin and corpuscles followed by reincubation in a water-bath for one hour. The results were recorded after the tubes had stood for the settling of corpuscles.

The different antigens and primary incubations employed in these experiments are shown in the accompanying tables and charts.

Additional experiments were conducted by incubating five units of each antigen with increasing amounts of complement as one, two, three, four and five hemolytic units; after primary incubation the amount of complement fixation or inactivation was determined by adding one unit of hemolysin and sheep corpuscles and reincubating in a water-bath for one hour. The different kinds of incubation used are given in Chart 2.

*Results.*—The results of titrations with a cholesterolized (0.4 per cent) alcoholic extract of beef heart are shown in Table I; with a plain or crude alcoholic extract of beef heart in Table II; with a





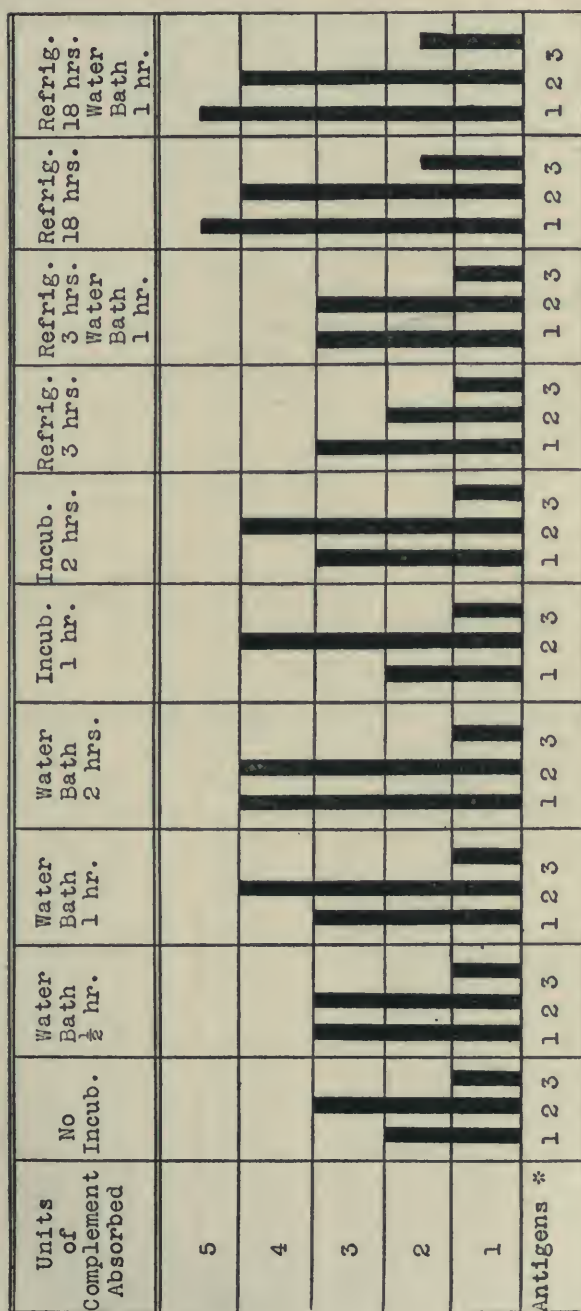


Chart 2.—The influence of temperature and duration of primary incubation upon the anticomplementary activity of organ extracts (antigens).  
 \*Antigens: 1—cholesterolized alcoholic extract of beef heart (0.4 per cent cholesterol).  
 2—plain or crude alcoholic extract of beef heart.  
 3—acetone-insoluble lipoids of beef heart.

plain alcoholic extract of syphilitic liver in Table III and with an extract of acetone insoluble lipoids of beef heart in Table IV. The tables show the 17 different kinds of primary incubation used with each antigen. The results with the cholesterolized and plain alcoholic extracts of beef heart and with the extract of acetone-insoluble lipoids have been summarized graphically in Chart 1, to show at a glance the tremendous influence exerted upon the nonspecific fixation of complement by these different antigens at varying temperatures. In this chart, 4 indicates the complete fixation of complement in these experiments and the results have been plotted accordingly.

Chart 2 shows in a graphic manner the amount of complement absorbed as measured in units by three different extracts, namely, a cholesterolized and plain alcoholic extract of beef heart and an extract of acetone-insoluble lipoids; nine different kinds of primary incubation were used and the results have proved interesting and instructive.

TABLE I

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON  
THE ANTICOMPLEMENTARY ACTIVITY OF CHOLESTERIZED  
EXTRACT OF HEART MUSCLE

PRIMARY INCUBATION		RESULTS WITH ANTIGEN 1:10					
TEMPERATURE	TIME	0.1	0.2	0.4	0.6	0.8	1.0
37° C. (incubator)	½ hr.	—*	—	—	—	—	—
38° C. (water-bath)	½ hr.	—	—	1	2	1	—
37° C. (incubator)	1 hr.	—	—	—	—	—	—
38° C. (water-bath)	1 hr.	—	1	3	4	4	4
37° C. (incubator)	2 hrs.	—	1	2	3	1	—
38° C. (water-bath)	2 hrs.	2	2	3	4	4	4
23° C. (room)	4 hrs.	—	—	1	2	1	—
8° C. (refrigerator)	2 hrs.	—	—	—	—	—	—
8° C. (refrigerator)	3 hrs.	—	—	—	—	—	—
8° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
2° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
0° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
8° C. (refrigerator) + (water-bath)	2 + 1 hr.	—	2	3	3	2	—
8° C. (refrigerator) + (water-bath)	3 + 1 hr.	—	—	3	3	3	2
8° C. (refrigerator)	18 hrs.	3	4	4	4	4	3
8° C. (refrigerator) + (water-bath)	18 + ½ hr.	4	4	4	4	4	4
8° C. (refrigerator) + (water-bath)	18 + 1 hr.	4	4	4	4	4	4

\*— = Complete hemolysis; 1 = 25 per cent inhibition of hemolysis; 2 = 50 per cent inhibition; 3 = 75 per cent inhibition; 4 = 100 per cent inhibition.



TABLE II

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON  
THE ANTICOMPLEMENTARY ACTIVITY OF PLAIN OR CRUDE  
ALCOHOLIC EXTRACT OF HEART MUSCLE

PRIMARY INCUBATION		RESULTS WITH ANTIGEN 1:10					
TEMPERATURE	TIME	0.1	0.2	0.4	0.6	0.8	1.0
37° C. (incubator)	½ hr.	—*	—	—	—	—	—
38° C. (water-bath)	½ hr.	—	—	—	—	—	—
37° C. (incubator)	1 hr.	—	—	—	—	—	1
38° C. (water-bath)	1 hr.	—	—	—	—	1	2
37° C. (incubator)	2 hrs.	—	—	—	—	1	2
38° C. (water-bath)	2 hrs.	—	—	4	4	3	3
23° C. (room)	4 hrs.	—	—	—	—	1	1
8° C. (refrigerator)	2 hrs.	—	—	—	—	—	1
8° C. (refrigerator)	3 hrs.	—	—	—	—	—	—
8° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
2° C. (refrigerator)	4 hrs.	—	—	—	—	1	1
0° C. (refrigerator)	4 hrs.	—	—	—	—	1	1
8° C. (refrigerator) + (water-bath)	2 + 1 hr.	—	—	—	—	2	2
8° C. (refrigerator) + (water-bath)	3 + 1 hr.	—	—	—	—	2	2
8° C. (refrigerator)	18 hrs.	—	—	—	1	1	2
8° C. (refrigerator) + (water-bath)	18 + ½ hr.	—	—	—	1	3	4
8° C. (refrigerator) + (water-bath)	18 + 1 hr.	—	—	1	2	3	4

\* = complete hemolysis; 1 = 25 per cent inhibition of hemolysis; 2 = 50 per cent inhibition; 3 = 75 per cent inhibition; 4 = 100 per cent inhibition.

TABLE III

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON  
THE ANTICOMPLEMENTARY ACTIVITY OF PLAIN ALCOHOLIC  
EXTRACT OF SYPHILITIC LIVER

PRIMARY INCUBATION		RESULTS WITH ANTIGEN 1:10					
TEMPERATURE	TIME	0.1	0.2	0.4	0.6	0.8	1.0
37° C. (incubator)	½ hr.	—*	—	—	—	—	—
38° C. (water-bath)	½ hr.	—	—	—	1	2	2
37° C. (incubator)	1 hr.	—	—	—	1	2	1
38° C. (water-bath)	1 hr.	—	—	1	2	3	3
37° C. (incubator)	2 hrs.	—	—	—	1	4	3
38° C. (water-bath)	2 hrs.	—	—	3	3	4	4
23° C. (room)	4 hrs.	—	—	—	—	1	1
8° C. (refrigerator)	2 hrs.	—	—	—	1	2	1
8° C. (refrigerator)	3 hrs.	—	—	—	—	2	3
8° C. (refrigerator)	4 hrs.	—	—	—	—	2	3
2° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
0° C. (refrigerator)	4 hrs.	—	—	—	—	—	—
8° C. (refrigerator) + (water-bath)	2 + 1 hr.	—	—	1	2	4	4
8° C. (refrigerator) + (water-bath)	3 + 1 hr.	—	—	1	2	3	4
8° C. (refrigerator)	18 hrs.	—	—	1	2	3	4
8° C. (refrigerator) + (water-bath)	18 + ½ hr.	—	1	3	4	4	4
8° C. (refrigerator) + (water-bath)	18 + 1 hr.	—	1	3	4	4	4

\* = complete hemolysis; 1 = 25 per cent inhibition of hemolysis; 2 = 50 per cent inhibition; 3 = 75 per cent inhibition; 4 = 100 per cent inhibition.

TABLE IV

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON  
THE ANTICOMPLEMENTARY ACTIVITY OF AN EXTRACT OF  
ACETONE-INSOLUBLE LIPIDS

PRIMARY INCUBATION		RESULTS WITH ANTIGEN 1:10					
TEMPERATURE	TIME	0.1	0.2	0.4	0.6	0.8	1.0
37° C. (incubator)	½ hr.	—*	—	—	—	1	2
38° C. (water-bath)	½ hr.	—	—	—	1	2	2
37° C. (incubator)	1 hr.	—	—	—	1	3	3
38° C. (water-bath)	1 hr.	—	—	—	1	2	3
37° C. (incubator)	2 hrs.	—	—	3	4	4	4
38° C. (water-bath)	2 hrs.	—	3	3	4	4	4
23° C. (room)	4 hrs.	—	—	1	2	3	4
8° C. (refrigerator)	2 hrs.	—	—	—	1	3	4
8° C. (refrigerator)	3 hrs.	—	—	—	—	3	4
8° C. (refrigerator)	4 hrs.	—	—	—	2	4	4
2° C. (refrigerator)	4 hrs.	—	—	1	2	4	4
0° C. (refrigerator)	4 hrs.	—	—	1	2	3	4
8° C. (refrigerator) + (water-bath)	2 + 1 hr.	—	—	—	1	4	4
8° C. (refrigerator) + (water-bath)	3 + 1 hr.	—	—	1	2	4	4
8° C. (refrigerator)	18 hrs.	—	1	4	4	4	4
8° C. (refrigerator) + (water-bath)	18 + ½ hr.	—	1	3	4	4	4
8° C. (refrigerator) + (water-bath)	18 + 1 hr.	—	1	3	4	4	4

\*- = complete hemolysis; 1 = 25 per cent inhibition of hemolysis; 2 = 50 per cent inhibition; 3 = 75 per cent inhibition; 4 = 100 per cent inhibition.

The results of these experiments may be summarized as follows:

1. Temperature influences the anticomplementary activities of organ extracts differently according to the kind of extract.

2. At 37° to 38° C. the anticomplementary activity of the antigens tested was slight with a primary incubation of one-half hour, but became marked at the end of one hour and slightly more so after two hours; incubation in an open water-bath at 38° C. generally resulted in greater nonspecific fixation or inactivation of complement than in an air incubator at 37° C.

3. At 0° to 8° C. for four hours the cholesterolized and plain alcoholic extracts were practically without anticomplementary activity, although the extract of acetone-insoluble lipoids absorbed slightly more complement than at 37° to 38° C. for one hour.

4. At 8° C. for eighteen hours the cholesterolized extract and extract of acetone-insoluble lipoids become markedly anticomplementary, while the plain extracts of beef heart and syphilitic liver remain free or nearly so.

5. Incubation in a water-bath at 38° C. for one-half to one hour following incubation at 8° C. for two to eighteen hours increased the anticomplementary activity of all antigens and particularly the cholesterolized extract.

These experiments show therefore, *that primary incubation at 8° C. for approximately eighteen hours greatly increases the nonspecific fixation of complement by antigen alone, particularly by cholesterolized extract and least by plain or crude alcoholic extracts; the stronger Wassermann reactions observed after cold incubation are due in part to this nonspecific fixation and may explain the pseudopositive reactions observed by some investigators with normal sera in tests conducted with cholesterolized extracts and incubation of about eighteen hours at 8° to 10° C.*

## Part 2

### THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE ANTICOMPLEMENTARY ACTIVITY OF HEATED HUMAN SERA

*Technic.*—In conducting these experiments guinea pig complement was titrated as described above and used in two units.

Sera were selected of varying ages, heated at 55° C. for fifteen minutes and used in amounts varying from 0.01 to 0.2 c.c. with two units of complement; these mixtures were kept at varying temperatures for varying periods of time when one unit of hemolysin and sheep corpuscles were added followed by reincubation in a water-bath for one hour to detect the effects of the sera upon complement according to the degree of hemolysis.

The fourteen different kinds of primary incubation employed are shown in Chart 3.

Additional experiments were conducted by using heated sera in constant amounts of 0.1 c.c. with increasing amounts of complement as one, two, three and four units; after primary incubation one unit of hemolysin and sheep corpuscles were added followed by reincubation in a water-bath for one hour. A summary of the results observed with three sera are shown graphically in Chart 4, indicating the influence of temperature and duration of primary incubation upon the absorption or fixation of complement by sera.

*Results.*—As expected, these varied according to the freshness of the sera and the presence or absence of thermolabile and thermostabile



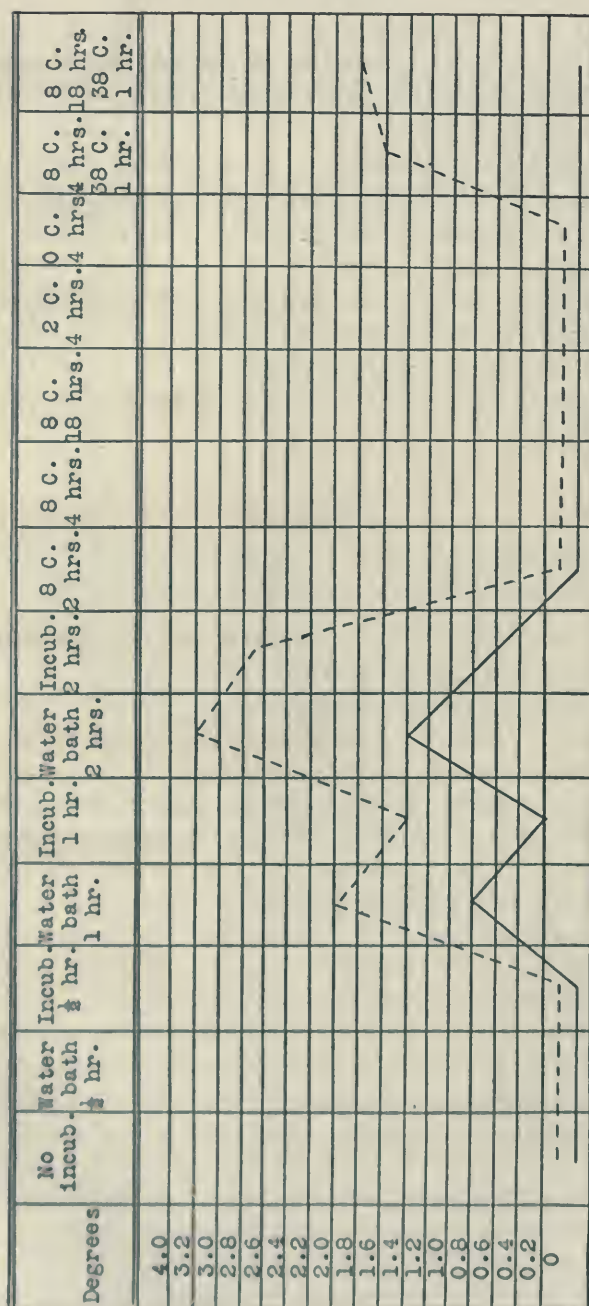


Chart 3.—The influence of temperature and duration of primary incubation upon the nonspecific fixation of complement by sera (anticomplementary activity of sera).  
 — with a serum three days old.  
 - - - - - with a serum about seven days old and kept at 8° C.; this serum was clear but contained bacteria upon culture.



Units of Complement Absorbed	No Incub.	Water Bath $\frac{1}{2}$ hr.	Water Bath 1 hr.	Water Bath 2 hrs.	Incub. 1 hr.	Incub. 2 hrs.	Refrig. 3 hrs. Water Bath 1 hr.	Refrig. 3 hrs. Water Bath 1 hr.	Refrig. 18 hrs. Water Bath 1 hr.
4									
$3\frac{1}{2}$									
3									
$2\frac{1}{2}$									
2									
$1\frac{1}{2}$									
1									

Chart 4.—The influence of temperature and duration of primary incubation upon the anticomplementary activity of human sera.

antilynsins; also according to the amounts of natural antisheep hemolysin present in each serum.

The majority of perfectly fresh sera yielded entirely negative results, that is, were free of anticomplementary activity; older sera and particularly those containing bacteria showed varying effects upon complement. Chart 3 shows the results observed with two sera of a series; one of these was quite fresh and the second older and more anticomplementary. In this chart, 4 represents the maximum of anticomplementary activity possible and the degrees of inhibition of hemolysis are plotted accordingly.

Chart 4 gives a graphic summary of the results observed with a third serum, the amount of complement absorbed in the different periods of primary incubation being measured in units.

The general results of these experiments have shown the following:

1. Incubation of serum and complement at 38° C. for one hour and particularly in a water-bath, may result in the inactivation or nonspecific fixation of considerable complement; the amount of this nonspecific fixation or inactivation is still greater after two hours' incubation.

2. *At 6° C. for four to eighteen hours there is practically no fixation or inactivation of complement by serum alone; heat and especially in the water-bath at 38° C., favors this phenomenon in a special manner.* For this reason, when sera are placed in a water-bath at 38° C. for an hour after a primary incubation at 8° C. for four to eighteen hours, a portion of the complement is fixed or inactivated by the antilynsins of the serum.

### Part 3

#### THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON NONSPECIFIC COMPLEMENT FIXATION BY NORMAL SERA AND VARIOUS ORGAN EXTRACTS WITH ESPECIAL REFERENCE TO CHOLESTEROLIZED EXTRACTS

As previously stated<sup>2</sup> some investigators and notably MacNeal, believe that complement-fixation tests conducted with cholesterolized extracts and a cold primary incubation may result in pseudo-positive reactions with the sera of nonsyphilitic persons, whereas plain or crude alcoholic extracts do not yield these nonspecific reactions. This very important subject is considered in detail in the

following paper of this series, devoted to the subject of antigen, but at present we wish to record the results of experiments conducted with a number of different organ extracts and the sera of healthy nonsyphilitic persons upon the special point of nonspecific complement fixation.

*Technic.*—Ten different extracts were employed with the sera of ten laboratory assistants with five different kinds of primary incubation; these details are shown in Table V giving the results observed with one serum. Each serum was about twenty-four hours old, heated at 55° C. for fifteen minutes and used in amount of 0.1 c.c. The complement was titrated in the presence of five antigenic units of each antigen and two units employed with one unit of antisyph hemolysin.

TABLE V  
THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON  
NONSPECIFIC COMPLEMENT FIXATION

ANTIGENS	UNIT COMPLEMENT 1:20	PRIMARY INCUBATION				
		WATER-BATH 38° C. 1 HR.	REFRIG. 8° C. 4 HRS.	REFRIG. 8° C. 4 HRS. WATER-BATH 1 HOUR	REFRIG. 8° C. 19 HRS.	REFRIG. 8° C. 19 HRS. WATER-BATH 1 HOUR
Cholest. human heart*	0.35	***	-	-	-	-
Cholest. beef heart**	0.5	-	-	±	+	+
Cholest. beef heart*	0.4	-	-	-	-	+
Plain beef heart*	0.35	-	-	-	-	-
Plain beef heart	0.2	-	-	-	-	-
Plain beef heart	0.25	-	-	-	-	+
Plain syph. liver	0.4	-	-	-	-	-
Acet. insol. lipoids	0.35	-	-	-	-	+
Acet. insol. lipoids	0.2	-	-	-	-	-
Acet. insol. lipoids	0.35	-	-	-	-	-
Serum control	-	-	-	-	-	±

\*0.2 per cent cholestrol.

\*\*0.4 per cent cholestrol.

\*\*\*- = negative; ± = doubtfully positive; + = very weakly positive.

*Results.*—The results observed with one of these sera shown in Table V, are examples of those observed with the remaining nine sera and may be summarized as follows:

1. An alcoholic extract of heart muscle with 0.4 per cent cholesterol gave no pseudopositive reactions with a primary incubation of four hours at 8° C. but slightly positive reactions with two sera (one of which is shown in Table V) with an additional hour in the



water-bath at 38° C. and after nineteen hours at 8° C. with and without an additional hour at 38° C.

2. Alcoholic extracts with 0.2 per cent cholesterol gave no pseudoreactions with primary incubations of four and nineteen hours at 8° C. but yielded weakly positive reactions with three of the ten sera when the mixtures were given an additional incubation of one hour at 38° C. in a water-bath; a plain alcoholic extract and an extract of acetone-insoluble lipoids yielded similar results.

*According to these results it would appear that complement-fixation tests conducted with any organ extract and normal serum may yield weakly positive reactions of nonspecific character when the primary incubation at 8° C. is more than four hours in duration plus an additional hour in the water-bath; at 8° C. alone for four hours or longer only extracts saturated with cholesterol (0.4 per cent) are likely to yield weakly positive reactions; extracts containing 0.2 per cent cholesterol do not yield more nonspecific reactions than plain extracts or extracts of acetone-insoluble lipoids. These reactions were probably due to the summation of the anticomplementary activities of the extracts and possibly to a lesser extent of some of the sera as described above.*

#### CONCLUSIONS

1. Temperatures of 37° to 38° C. particularly increase the non-specific fixation or inactivation of complement by organ extracts or antigens and sera, commonly designated as the anticomplementary activity of these substances.

2. Temperatures of 8° to 10° C. for four hours have no appreciable influence upon increasing the nonspecific fixation or inactivation of complement by various antigens.

3. Temperatures of 8° to 10° C. for eighteen hours greatly increase the anticomplementary activities of cholesterolized extracts and to a lesser extent of extracts of acetone-insoluble lipoids; there is less effect upon the anticomplementary activity of plain alcoholic extracts.

4. Temperatures of 8° to 10° C. for four to eighteen hours have little or no influence upon increasing the anticomplementary activities of heated human sera.

5. Heating in a water-bath at 38° C. following incubation at 8° to 10° C. for four to eighteen hours increases the anticomplementary activities of antigens and sera.



6. Nonspecific complement-fixation reactions with mixtures of normal nonsyphilitic sera and organ extracts were not observed except in combined cold and warm primary incubations as four to eighteen hours at 8° C. plus one hour in a water-bath at 38° C.; alcoholic extracts saturated with cholesterol (0.4 per cent) were found particularly likely to yield these reactions, whereas plain alcoholic extracts, extracts containing 0.2 per cent cholesterol and extracts of acetone-insoluble lipoids were usually free of these non-specific effects.

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# STUDIES IN THE STANDARDIZATION OF THE WASSER-MANN REACTION. XVI\*

THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE VELOCITY AND AMOUNT OF COMPLEMENT

FIXATION IN SYPHILIS WITH DIFFERENT ORGAN

EXTRACTS (ANTIGENS)

BY JOHN A. KOLMER, M.D., ANNA M. RULE AND ELIZABETH M. YAGLE,  
B.Sc., PHILADELPHIA, PA.

*From the Dermatological Research Laboratories of Philadelphia*

(Received for publication, June 1, 1920.)

AS STATED in previous articles <sup>1, 2</sup> the temperature and duration of primary incubation have an important influence upon the hemolytic activity of complement alone and likewise upon the anti-complementary activities of organ extracts and heated human sera. Unquestionably a primary incubation of eighteen hours at 2° to 10° C. results in stronger complement-fixation reactions with the majority of syphilitic sera than occurs in a water-bath or incubator at 38° C. for one hour; these stronger reactions are ascribed *in part* to the greater destruction of complement and greater absorption of complement by antigen alone than occurs at 38° C.

Aside from these nonspecific effects, it is possible that more complement is specifically fixed by antigen and antibody by prolonged cold incubation than in the usual warm incubation at 38° C. for one hour; however, the period of cold incubation greatly prolongs the time required for conducting diagnostic tests, so that it is a matter of considerable practical importance to determine by comparative tests whether shorter periods of primary incubation may not yield similar results.

## PURPOSES OF INVESTIGATION

With these objects in view we have studied the velocity and amount of complement fixation in syphilis with different antigens at the following temperatures, as bearing upon the choice of a

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

method for conducting the primary incubation in a standardized complement-fixation technic:

1. No primary incubation at all.
2. At 37° to 38° C. in open water-bath and air incubator.
3. At 20° to 23° C. in the laboratory.
4. At 0° to 10° C. in pans of water and ice and in a refrigerator.

*Technic.*—Only known syphilitic sera were used, each serum being heated at 55° C. for fifteen minutes and used in amounts ranging from 0.1 to 0.0015 c.c. with five antigenic units of each antigen.

Guinea pig complement was titrated in the presence of five units of antigen and employed in amounts equal to two units.

The various periods of primary incubation employed are given in the accompanying tables and charts; in order to avoid error, the same sera, antigens, and complements were used in each experiment with 8 to 17 different kinds of primary incubation in order to elicit differences in the degree of complement fixation due alone to the temperature and duration of primary incubation.

One unit of antish sheep hemolysin and sheep corpuscles was added after primary incubation and the secondary incubations conducted in a water-bath at 38° C. for one hour; in a few experiments an anti-human hemolytic system was employed.

In preparing the charts, 4 was taken as the maximum of complement fixation and the results plotted accordingly.

To determine more accurately the degree of complement fixation, experiments were conducted by using each serum in constant amount of 0.1 c.c. with 5 units of antigen and increasing amounts of complement as 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 units after the method of Browning and McKenzie; the units of complement fixed by antigen alone and serum alone were subtracted in order to determine the amounts fixed by mixtures of serum and antigen. The results of these experiments were very interesting and are summarized in Chart 7.

## Part 1

### THE VELOCITY OF COMPLEMENT FIXATION AT 38° C.

In Table I are given the reactions with 12 syphilitic sera tested with a cholesterolized extract and an antihuman hemolytic system with no primary incubation and with an incubation in a water-bath at 38° C. for five, fifteen, thirty and sixty minutes.

TABLE I  
THE RATE OF COMPLEMENT FIXATION AT 38° C. IN A WATER-BATH\*

SERA	NO PRIMARY INCUBATION			5 MINUTES 38° C.			15 MINUTES 38° C.			30 MINUTES 38° C.			60 MINUTES 38° C.		
	0.1	0.01	0.001	0.0001	C	0.1	0.01	0.001	0.0001	C	0.1	0.01	0.001	0.0001	C
1	1	—	—	—	—	3	1	—	—	—	4	3	—	—	—
2	—	—	—	—	—	4	3	—	—	—	4	4	1	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4	1	—	—	—	—	4	2	—	—	—	4	2	—	—	—
5	—	—	—	—	—	4	—	—	—	—	4	2	—	—	—
6	1	—	—	—	—	4	1	—	—	—	4	3	—	—	—
7	1	—	—	—	—	4	1	—	—	—	4	1	—	—	—
8	1	—	—	—	—	2	1	—	—	—	4	1	—	—	—
9	1	—	—	—	—	2	1	—	—	—	4	1	—	—	—
10	1	—	—	—	—	2	2	—	—	—	2	2	—	—	—
11	2	—	—	—	—	4	3	—	—	—	4	4	—	—	—
12	4	2	—	—	—	4	4	1	—	—	4	4	1	—	—

\* All tests conducted with heated sera, a cholesterolized extract and an antihuman hemolytic system.



TABLE II  
THE RAPIDITY OF COMPLEMENT FIXATION IN SYPHILIS AT DIFFERENT TEMPERATURES\*

PRIMARY INCUBATION	SERUM I.					SERUM II.				
	0.1	0.025	0.006	0.0015	C	0.1	0.025	0.006	0.0015	C
No incubation.....	3**	3	—	—	—	3	2	—	—	—
38° C. water-bath, 5 minutes.....	3	3	—	—	—	3	2	—	—	—
38° C. water-bath, 15 minutes.....	4	3	—	—	—	3	3	—	—	—
38° C. water-bath, 30 minutes.....	4	4	1	—	—	4	4	1	—	—
38° C. water-bath, 45 minutes.....	4	4	1	—	—	4	4	1	—	—
38° C. water-bath, 1 hour.....	4	4	1	—	—	4	4	1	—	—
38° C. water-bath, 1½ hours.....	4	4	1	—	—	4	4	1	—	—
38° C. water-bath, 2 hours.....	4	4	1	—	—	4	4	1	—	—
8° C. refrigerator, 15 minutes.....	4	3	—	—	—	3	3	—	—	—
8° C. refrigerator, 30 minutes.....	4	4	1	—	—	3	3	—	—	—
8° C. refrigerator, 1 hour.....	4	4	1	—	—	4	4	—	—	—
8° C. refrigerator, 2 hours.....	4	4	1	—	—	4	4	1	—	—
8° C. refrigerator, 3 hours.....	4	4	1	—	—	4	4	1	—	—
8° C. refrigerator, 4 hours.....	4	4	2	—	—	4	4	1	—	—
2° C. ice and water, 15 minutes.....	3	3	—	—	—	3	2	—	—	—
2° C. ice and water, 30 minutes.....	3	3	1	—	—	3	3	—	—	—
2° C. ice and water, 1 hour.....	4	4	1	—	—	3	3	1	—	—
2° C. ice and water, 2 hours.....	4	4	3	—	—	4	4	—	—	—
2° C. ice and water, 3 hours.....	4	4	3	—	—	4	4	1	—	—
2° C. ice and water, 4 hours.....	4	4	3	—	—	4	4	1	—	—

\* Tests conducted with an extract containing 0.2 per cent cholesterol; antiseptic system.

\*\* 4 = + + + + +; 3 = + + + +; 2 = + +; 1 = +.

Table II shows the reactions with two additional sera tested with a cholesterolized extract and water-bath incubation of five, fifteen, thirty, forty-five, sixty, ninety, and one hundred and twenty minutes.

Chart 1 gives a summary of the reactions observed with 24 syphilitic sera tested with an extract of acetone-insoluble lipoids with primary incubations in a water-bath of five, fifteen, thirty, forty-five and sixty minutes; Chart 2 gives a summary of reactions with 12 additional sera tested simultaneously with a plain and cholesterolized extract with primary incubations in a water-bath of five

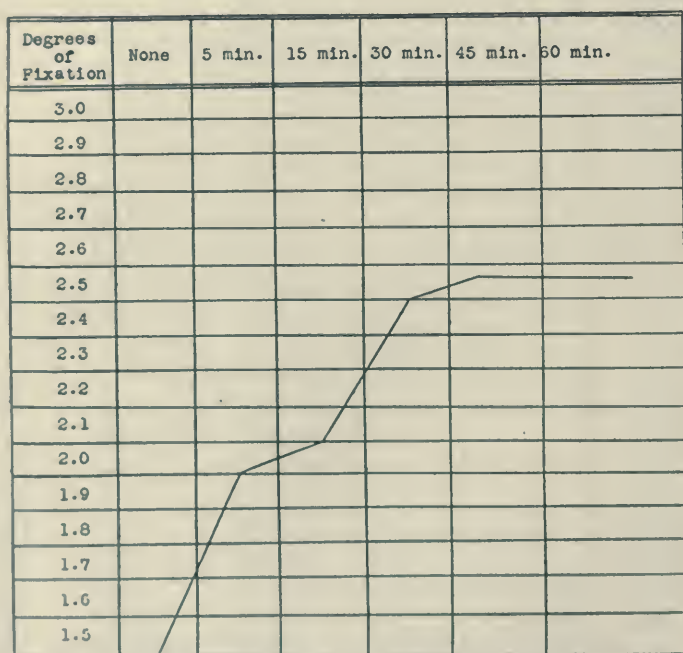


Chart 1.—Curve of complement-fixation with a primary incubation at 38° C. in a water-bath. Extract of acetone-insoluble lipoids.

minutes to three hours. Chart 3 is a summary of reactions with 6 sera tested with a plain and cholesterolized extract with primary incubations in a water-bath and air incubator of fifteen minutes to two hours.

The results of these experiments may be summarized as follows:

1. Complement fixation with strongly syphilitic sera used undiluted in amount of 0.1 c.c. is frequently very rapid and may occur

within a few minutes at room temperature (20° to 23° C.) with no primary incubation at all; this is especially true when cholesterolized extracts and extracts of acetone-insoluble lipoids are employed. Incubation at 38° C., however, usually increases the degree of complement fixation.

2. Complement-fixation is usually but not always more rapid in a water-bath at 38° C. than in an air incubator at the same temperature, as determined by comparative tests with incubations varying from fifteen minutes to two hours (Chart 3). This is true with both plain and cholesterolized extracts.

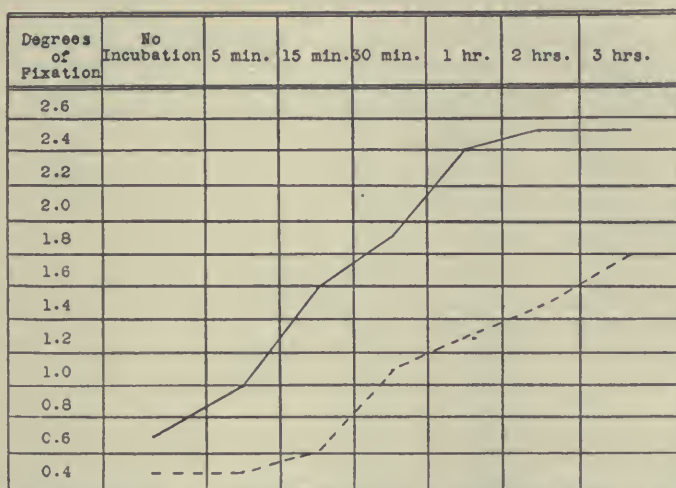


Chart 2.—The velocity of complement-fixation in a water-bath at 38° C. with cholesterolized and plain antigens.

———— = curve with a cholesterolized (0.2 per cent) alcoholic extract of heart muscle.  
 - - - - - = curve with a plain alcoholic extract of heart muscle.

*With these antigens, however, one-half hour in a water-bath is scarcely equal to one hour in the incubator, as is commonly stated to be the case.*

3. Incubations at 38° C. for more than two hours are frequently unsatisfactory with tests conducted with two units of complement because sufficient inactivation or destruction of complement occurs under these conditions to produce incomplete hemolysis of the serum and antigen controls.

4. The velocity of complement fixation in syphilis at 38° C. varies with the kind of antigen employed, being most rapid with cholesterolized extracts and least with plain or crude extracts.

5. In general terms complement fixation reaches the maximum degree at 38° C. in a water-bath with extracts of acetone-insoluble lipoids in from thirty to forty-five minutes; with cholesterolized extracts in one to two hours and with plain or crude alcoholic extracts at least two to three hours are required.

## Part 2

### THE VELOCITY OF COMPLEMENT FIXATION AT 20° C.

Chart 3 gives a summary of the results observed with six syphilitic sera tested with plain and cholesterolized alcoholic extracts of

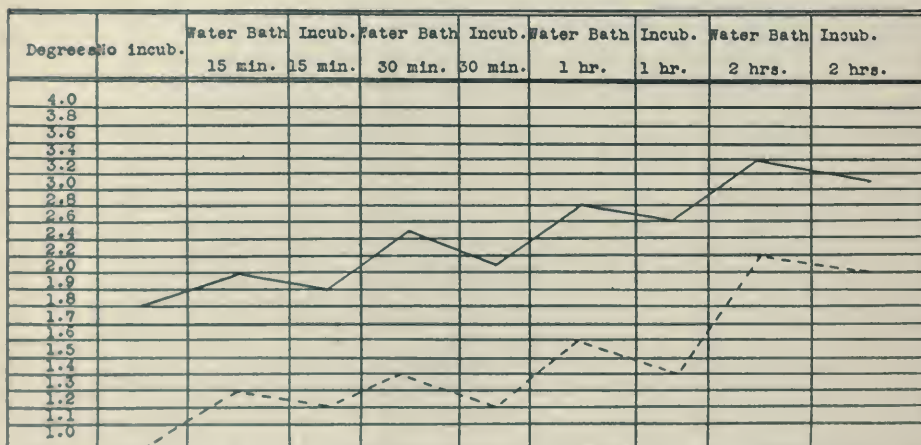


Chart 3.—The velocity of complement-fixation at 38°C. in a water-bath and air incubator with plain and cholesterolized antigens.

— = curve of fixation with a cholesterolized extract (0.2 per cent).

----- = curve of fixation with a plain extract.

beef heart with periods of primary incubation at 20° C. (room) and 38° C. (water-bath) varying from fifteen minutes to three hours; longer periods could not be used because of deterioration of sufficient complement at 38° C. after two hours and at 20° C. after three hours, to yield incomplete hemolysis of the serum and antigen controls.

Water-bath incubation almost always resulted in more fixation of complement than occurred at room temperature when equal periods of primary incubation are compared; fixation of complement occurs more slowly at 20° C. than at 38° C. under these circumstances.

Primary incubation of one hour in a room at 20° C. results in less



complement fixation than occurs in one-half hour in a water-bath at 38° C. *but in general terms two hours at 20° C. results in fixation about equal to one hour at 38° C.*

### Part 3

#### THE VELOCITY OF COMPLEMENT FIXATION AT 0°-15° C.

The temperature of the lower compartments of an ordinary ice refrigerator varies from 6° to 10° C. with an average of 8° C.; in the ice chamber and with racks of tubes placed on cakes of ice, a temperature of about 2° C. is usually observed. Open pans of water and ice are readily adjusted to 2° C. and maintained for several hours with an occasional inspection and addition of ice. With mixtures of water, ice and salt the temperature can be reduced to 0° C. and lower.

We have determined the velocity of complement fixation at temperatures varying from 0° to 15° C., but with special reference to 0°-2° C. and 8°-10° C.; the former temperature was secured in open pans of water and ice and the latter in an ordinary ice refrigerator.

Table III presents the results observed with twelve syphilitic sera tested with a cholesterolized extract with periods of primary incubation at 2° C. varying from one-half to four hours; Table IV is a similar study with twelve other sera with primary incubations at 8° to 10° C.

Chart 5 gives a summary of complement-fixation reactions with 12 syphilitic sera tested with a cholesterolized extract with periods of primary incubation of three hours' duration at temperatures varying from 0° to 20° C.; an additional period of twenty-one hours at 8° C. is included.

Chart 6 gives a summary of complement-fixation reactions with 12 syphilitic sera tested with a cholesterolized extract at 2° and 8° C. for periods varying from one-half to eighteen hours.

In these charts, 4 represents the maximum of fixation possible, and the degrees of fixation are plotted accordingly.

The results of these experiments may be summarized as follows:

1. Complement fixation at low temperatures (0° to 8° C.) is surprisingly rapid, well-marked reactions being observed even after incubations of but fifteen minutes.

2. Complement fixation in syphilis occurs somewhat more rapidly at 8° C. than at 0° to 2° C.; in general terms four hours at 2° C.

TABLE III  
THE RAPIDITY OF COMPLEMENT FIXATION IN SYPHILIS AT 20° C. \*

SERA	½ HOUR			1 HOUR			2 HOURS			3 HOURS			4 HOURS		
	0.1 0.025 0.006 0.0015 C			0.1 0.025 0.006 0.0015 C			0.1 0.025 0.006 0.0015 C			0.1 0.025 0.006 0.0015 C			0.1 0.025 0.006 0.0015 C		
	4	2	1	4	2	1	4	2	1	4	2	1	4	2	1
1	4	3	—	4	4	—	4	4	1	4	4	1	4	1	—
2	2	1	—	4	4	—	4	4	—	4	4	—	4	4	—
3	4	4	—	4	4	—	4	4	1	4	4	1	4	1	—
4	4	4	—	4	4	—	4	4	1	4	4	1	4	2	—
5	4	4	—	4	4	—	4	4	1	4	4	1	4	1	—
6	4	4	—	4	4	—	4	4	1	4	4	1	4	1	—
7	4	4	—	4	4	—	4	4	1	4	4	1	4	1	—
8	4	4	—	4	4	—	4	4	1	4	4	1	4	3	—
9	4	4	—	4	4	—	4	4	1	4	4	1	4	4	—
10	3	1	—	3	1	—	3	3	—	3	3	—	3	—	—
11	4	4	—	4	4	—	4	4	—	4	4	—	4	4	—
12	4	4	—	4	4	—	4	4	—	4	4	—	4	4	—

\* Antisheep system; cholesterolized extract (0.2 per cent).

TABLE IV  
THE RAPIDITY OF COMPLEMENT FIXATION IN SYPHILIS AT 8° TO 10° C. \*

SERA	1/2 HOUR					1 HOUR					2 HOURS					3 HOURS					4 HOURS					18 HOURS				
	0.1	0.025	0.006	0.0015	C	0.1	0.025	0.006	0.0015	C	0.1	0.025	0.006	0.0015	C	0.1	0.025	0.006	0.0015	C	0.1	0.025	0.006	0.0015	C					
1	4	3	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
2	4	4	2	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
3	4	4	4	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
4	4	4	4	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
5	3	3	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
6	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
7	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
8	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
9	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
10	3	1	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
11	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					
12	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—					

\* Antisheep system; cholesterolized extract. (0.2 per cent.)

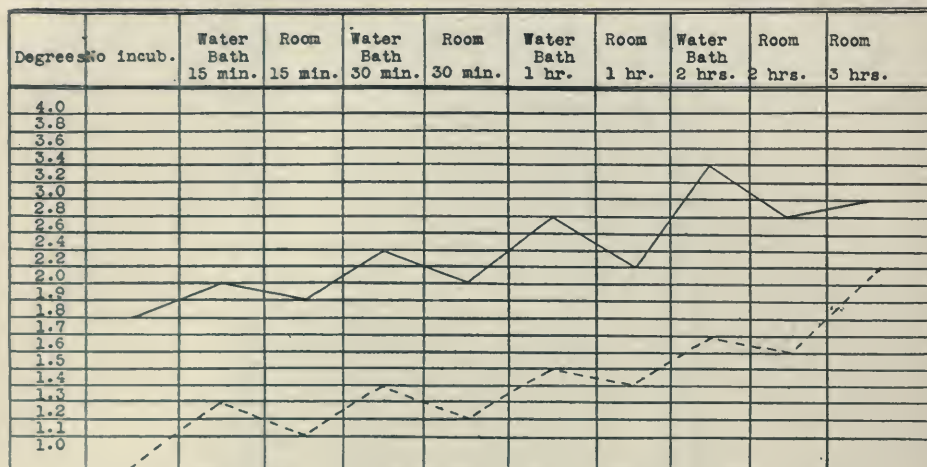


Chart 4.—The velocity of complement-fixation at room temperature (20° C.) with plain and cholesterolized extracts.

— = curve of fixation with a cholesterolized extract (0.2 per cent).  
 ---- = curve of fixation with a plain extract.

yields the same or slightly greater fixation of complement than occurs in two hours at 8° C. (Chart 6).

3. The optimum temperature for complement fixation in syphilis with cold incubation is from 6° to 15° C.; with a period of three hours, more complement is fixed at 2° C. than at 0° C. and more at 6° C. than at 2° C.; at 6° to 15° C. there is practically no difference in the degree of fixation although at 20° C. (room), slightly stronger reactions are observed which, however, are frequently due to destruc-

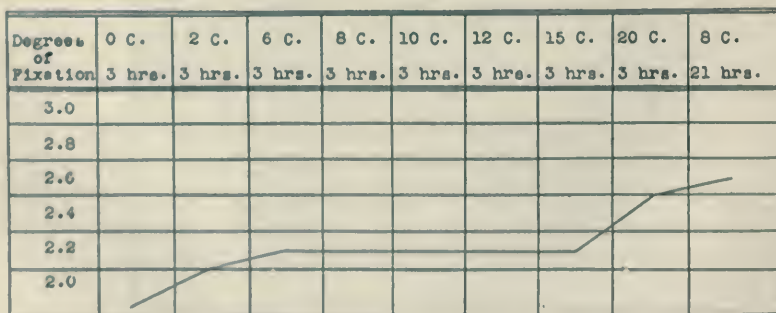


Chart 5.—Curve of complement-fixation in syphilis at temperatures 0° to 20° C. Tests conducted with an alcoholic extract containing 0.2 per cent cholesterolin.



tion or inactivation of complement rather than specific fixation of complement (Chart 5).

4. *Water-bath incubation at 38° C. for one-half to one hour results in the fixation of more complement than at 2° to 8° C. in three hours but less than occurs at 8° C. for three hours plus one hour in a water-bath and much less than at 2° to 8° C. for eighteen hours. This is apparently true with both plain and cholesterolized extracts and extracts of acetone-insoluble lipoids.*

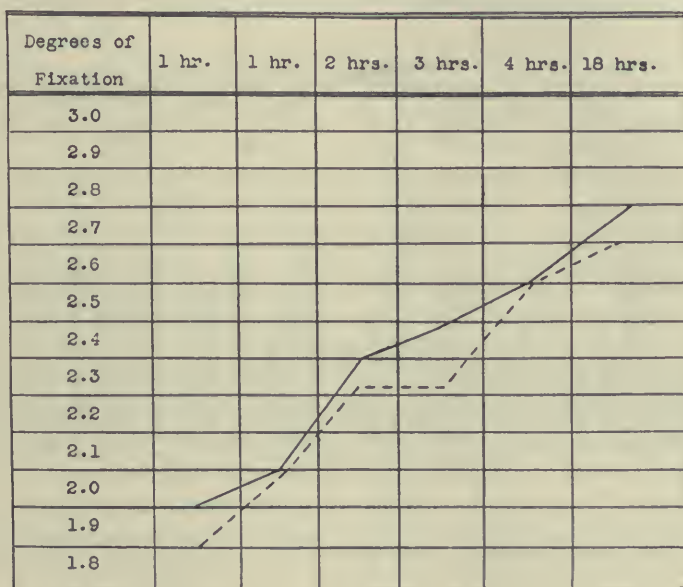


Chart 6.—Curves of complement-fixation at 2° C. and 8° C. with an alcoholic extraction of heart containing 0.2 per cent cholesterolin.

———— = Fixation at 8° C. in a refrigerator.

----- = Fixation at 2° C. in a pan of ice and water.

#### Part 4

##### THE INFLUENCE OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION UPON THE AMOUNT OF COMPLEMENT FIXED BY SYPHILITIC SERA AND ANTIGEN

By reason of the influence of temperature and duration of primary incubation upon complement alone<sup>1</sup> and more especially upon the anticomplementary effects of organ extracts and sera alone,<sup>2</sup> the technic of Browning and McKenzie has been found very useful for

determining the influence of temperature upon the fixation of complement by mixtures of syphilitic serum and extract; with a modification of this technic the amount of complement fixed by antigen alone and serum alone has been measured in units and subtracted from the number of units fixed by the mixture of the two.

The results of one experiment with a syphilitic serum and three different organ extracts are shown in Chart 7, that is, the amounts of complement expressed in units fixed by serum and antigen minus that fixed by these separately, are given for each of eight different primary incubations.

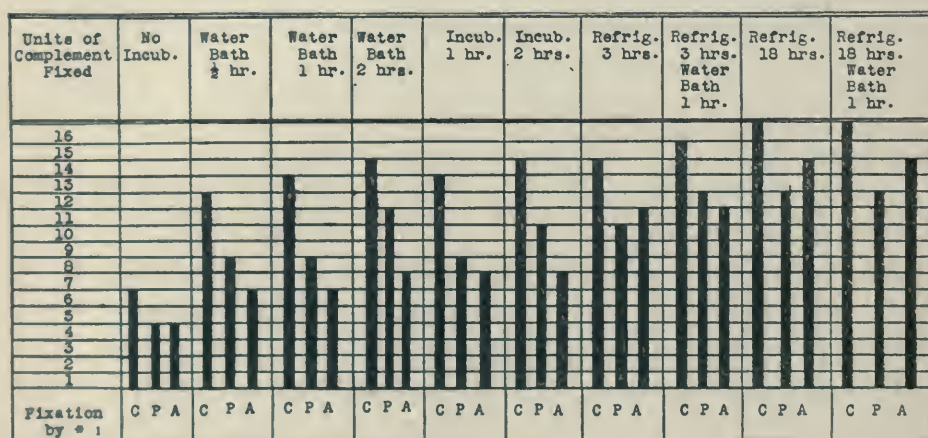


Chart 7.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units of syphilitic serum and three different antigens. C = cholesterolized extract; P = plain extract; A = acetone-insoluble lipoids.

The results of these experiments have shown:

1. With cholesterolized extracts complement fixation occurs more rapidly and to greater degree at all temperatures than with plain extracts; *cold incubation is especially favorable to complement fixation by plain alcoholic extracts and extracts of acetone-insoluble lipoids.*

2. Cold incubation at 8° C. for three to eighteen hours increases the amount of complement absorbed or fixed by mixtures of syphilitic serum and antigen; the stronger complement fixation reactions observed with all antigens at 8° C. are due not only to an increase of complement fixation by serum alone and antigen alone, *but also to an actual increase of specific fixation by mixtures of these.*

## Part 5

THE EFFECT OF TEMPERATURE AND DURATION OF PRIMARY INCUBATION  
UPON COMPLEMENT FIXATION WITH ESPECIAL REFERENCE TO  
THE KIND OF ORGAN EXTRACT EMPLOYED AS ANTIGEN

As shown in a previous article<sup>2</sup> the amount of complement fixed or absorbed by organ extracts alone varies with the kind of extract; as a general rule alcoholic extracts containing 0.4 per cent cholesterol absorbed or fixed more complement at different temperatures and particularly at 8° C. for eighteen hours, than plain extracts and extracts of acetone-insoluble lipoids.

MacNeal and others have found that cholesterolized extracts are most sensitive both at 8° and 38° C., but plain extracts are as sensitive as cholesterolized extracts when the primary incubation is conducted at 8° C. and that nonspecific reactions do not occur. Extracts of acetone-soluble lipoids were found inferior in antigenic sensitiveness to cholesterolized extracts both at 38° and 8° C.; compared with plain alcoholic extracts they were found inferior at 8° C. but superior at 38° C.

In other words while temperature influences the anticomplementary activity of an extract, it also appears to influence the antigenic sensitiveness, that is, an extract will apparently fix more complement with a syphilitic serum at one temperature than at another, the degree of anticomplementary activity of antigen and serum alone being constant. This is well shown in Chart 7 and in the following experiments.

*Technic.*—Only known syphilitic sera were employed and each in a fresh state to reduce to a minimum nonspecific fixation of complement by serum alone; each serum was heated at 55° C. for fifteen minutes and used in amounts varying from 0.1 to 0.0004 c.c. to elicit differences in antigenic sensitiveness of the extracts.

Each extract was carefully titrated for anticomplementary and antigenic units and used in doses of five antigenic units; each complement was titrated in the presence of antigen and used in dose of two units. After primary incubation, one unit of hemolysin and sheep corpuscles were added and the tubes re-incubated at 38° C. for one hour, the readings being made after the tubes had stood for the settling of cells.

*Results.*—Results are best expressed graphically in charts; in these



charts, 4 represents the maximum degree of complement fixation and the curves are plotted accordingly.

Chart 8 summarizes the results observed with 24 syphilitic sera tested with a plain and cholesterolized alcoholic extract of beef heart in a primary of one hour at 38° C. in a water-bath and in a refrigerator at 10° C. for one-half to nineteen hours.

Chart 9 presents a summary of the reactions observed with

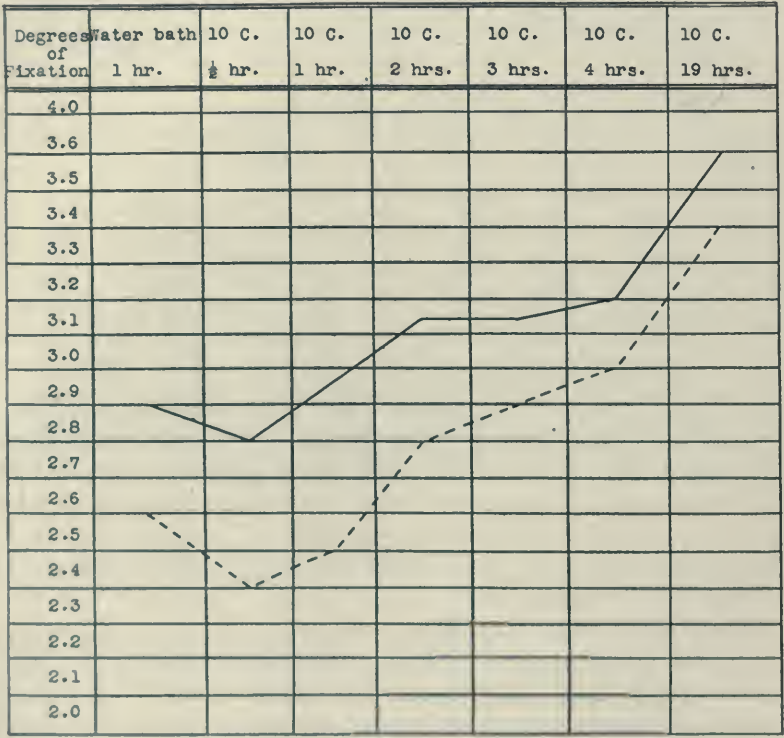


Chart 8.—Complement-fixation at 10° C.  
———— = with a cholesterolized alcoholic extract of beef heart.  
----- = with a plain alcoholic extract of beef heart.

twelve syphilitic sera tested with plain and cholesterolized extracts with five different kinds of primary incubation; Chart 10 is a similar study with six sera in six different kinds of incubation.

Chart 11 presents a summary of the results observed with six syphilitic sera tested at the same time with 3 different antigens in 17 different kinds of primary incubation.



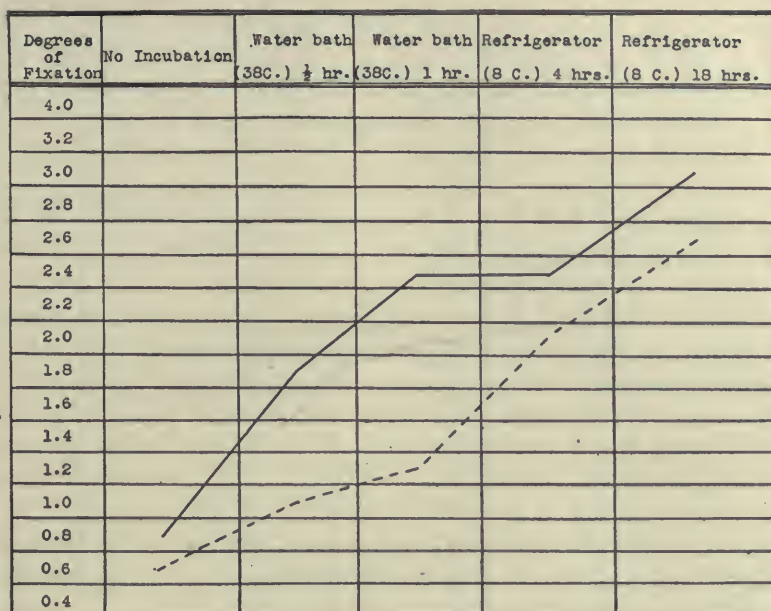


Chart 9.—The influence of temperature upon complement-fixation with plain and cholesterolized extracts.

———— = curve with a cholesterolized alcoholic extract of heart muscle.  
 ---- = curve with a plain alcoholic extract of heart muscle.

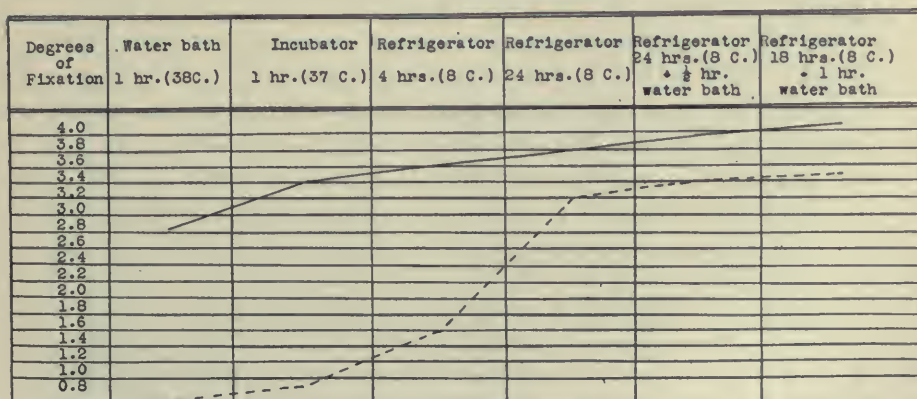


Chart 10.—The influence of temperature upon complement-fixation in syphilis with plain and cholesterolized organ extracts.

———— = with a cholesterolized alcoholic extract of beef heart.  
 ---- = with a plain alcoholic extract of beef heart.



The results of these experiments may be summarized as follows:

1. With a primary incubation in an incubator or water-bath at 38° C. for one-half to two hours, complement fixation occurs much more rapidly and completely with cholesterolized extracts and acetone-insoluble lipoids than with plain extracts of heart muscle and syphilitic liver.

2. With primary incubation at 8° C. the degree of complement fixation with the four different antigens is more nearly equal, that is, the antigenic sensitiveness of the plain extracts is increased to a much greater degree than the cholesterolized extracts and extracts of acetone-insoluble lipoids; in incubations at 8° C. for sixteen to twenty-four hours the antigenic sensitiveness of plain extracts of heart muscle and syphilitic liver "pick up" in a remarkable manner, but even at best are not quite equal in antigenic activity to cholesterolized extracts.

3. In primary incubations of four hours at 8° C. plus one hour in the water-bath at 38° C. plain extracts are much inferior in antigenic sensitiveness to cholesterolized extracts and acetone-insoluble lipoids.

4. Incubations of one hour in a water-bath at 38° C. do not result in the fixation of as much complement as in incubations of three hours at 8° C. plus one hour at 38° C. or as in incubations of eighteen hours at 8° C. This is especially true of plain extracts.

5. Incubations of two hours in a water-bath at 38° C. results in the fixation of about as much complement as occurs at 8° C. in eighteen hours with cholesterolized extracts and extracts of acetone-insoluble lipoids, but not with plain extracts.

Briefly, *complement fixation in syphilis with plain or crude alcoholic extracts of heart or luetic liver requires a primary incubation of at least eighteen hours at 8° C. to reach the maximum degree of fixation whereas with cholesterolized extracts and acetone-insoluble lipoids practically the same degree of fixation occurs after three hours at 8° C. plus one hour at 38° C. or two hours at 38° C.*

*In other words cold incubation favors fixation of complement with plain extracts more than warm incubation.*

#### CONCLUSIONS

1. Complement fixation with strongly syphilitic sera is frequently very rapid and may occur immediately at room temperature and especially with cholesterolized and acetone-insoluble lipid extracts as antigens; incubation at 38° C., however, usually increases the amount of complement fixation.



2. Complement fixation in syphilis is usually but not always, more complete in an open water-bath at 38° C. than in an air incubator at the same temperature; one-half hour in a water-bath, however, is not usually equal to one hour in an incubator, as is commonly stated.

3. The velocity and amount or degree of complement fixation at 38° C. varies greatly according to the organ extract used as antigen, being most rapid with cholesterolized extracts and least with plain or crude extracts.

4. In general terms complement fixation in syphilis reaches the maximum degree at 38° C. in a water-bath with extracts of acetone-insoluble lipoids in from 30 to 45 minutes; with cholesterolized extracts in one to two hours and with plain or crude alcoholic extracts at least two to three hours are required.

5. Primary incubation at 20° C. (room temperature) results in less complement fixation than in a water-bath at 38° C. for one-half hour; two hours at 20° C. results in a fixation of complement about equal to one hour at 38° C.

6. Complement fixation in syphilis at 0° to 8° C. is frequently very rapid, well marked reactions being observed even after incubations of but fifteen minutes.

7. At temperatures of 8° to 10° C. complement fixation in syphilis occurs more slowly than at 38° C. but the degree or amount of complement fixation is greater; this is especially true with plain or crude extracts.

8. Complement fixation in syphilis occurs somewhat more rapidly at 8° C. than at 0° to 2° C.; the optimum temperature for cold incubation is from 6° to 15° C. and the optimum time four to eighteen hours.

9. At 38° C. for one-half to two hours complement fixation in syphilis is much more rapid and greater in degree with cholesterolized and acetone-insoluble extracts as antigens than with plain or crude extracts; at 8° to 10° C. for about eighteen hours the difference in degree of complement fixation among the different extracts is not so marked, although the reactions with cholesterolized extracts are usually slightly stronger than with plain extracts.

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<sup>2</sup>Kolmer, J. A., and Trist, M. E.: The Influence of Temperature and Duration of Primary Incubation upon the Anticomplementary Activity of Organ Extracts (Antigens) and Sera, *Am. Jour. Syph.*, January, 1921, v, 30.



## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XVII\*

### A COMPARATIVE STUDY OF METHODS FOR CONDUCTING THE PRIMARY INCUBATION FOR COMPLEMENT FIXATION IN SYPHILIS WITH THE TECHNIC RECOMMENDED FOR A STANDARDIZED TEST

BY JOHN A. KOLMER, M.D., TOITSU MATSUNAMI, M.D., AND  
MARY E. TRIST, PHILADELPHIA, PA.

*From the Dermatological Research Laboratories of Philadelphia.*

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IN CONDUCTING the complement-fixation test for syphilis the following kinds of primary incubation for the fixation of complement are commonly employed:

Air incubation at 37° to 38° C. for one hour.

Water-bath at 38° C. for one-half hour.

Water-bath at 38° C. for one hour.

Refrigerator at 8° to 10° C. for four to twenty-four hours.

Refrigerator at 8° to 10° C. for several hours followed by water-bath for one-half to one hour.

As stated in previous articles,<sup>1, 2, 3</sup> the reactions following these different kinds of primary incubation are due to the influence of temperature and duration upon three factors, namely, (a) hemolytic activity of complement, (b) the nonspecific fixation of complement by antigens and sera alone and (c) the specific fixation of complement by mixtures of antigen and serum. Any primary incubation resulting in an increased destruction of complement or an increase of nonspecific fixation by antigen and serum alone, will necessarily result in stronger reactions, aside from the question of specific fixation.

Unquestionably incubation at 8° to 10° C. for eighteen hours increases the amount of nonspecific complement fixation by antigen and serum alone, but also results in an increase of specific fixation as compared with an incubation of one hour at 38° C.; this is especially true when plain antigens are employed. Accordingly stronger Wassermann reactions are usually observed with incuba-

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

tions of eighteen hours at 8° to 10° C. than after one hour at 37° to 38° C.

The ideal period of primary incubation is that which results in the least destruction of complement, the least nonspecific fixation of complement and the maximum specific fixation; a search for this involves a consideration of the kind of antigen employed and of practical working conditions, that is, the method must be applicable to the routine examination of large numbers of sera with a minimum of labor and time.

Aside from these considerations there remains the important one concerning the possibility of the existence of one kind of syphilis antibody fixing complement best at 38° C. and a second at lower temperatures; if these exist, the best complement-fixation work is only possible by conducting duplicate tests with each serum as suggested by Guggenheimer<sup>4</sup> and by Coea and L'Esperance<sup>5</sup> or, by a combined primary incubation of some hours at 8° to 10° C. followed by a period at 38° C., as suggested by Kaliski.

#### PURPOSES OF INVESTIGATION

Accordingly the purposes of this final study of the method of primary incubation for the complement-fixation reaction in syphilis, were as follows:

1. To determine whether two kinds of syphilis antibody exist insofar as concerns the fixation of complement at 38° C. and at 0°-10° C.
2. A comparative study of methods for the purpose of determining that which is best for routine complement-fixation tests.

#### Part 1

##### COMPLEMENT FIXATION IN SYPHILIS AT 37° C. AND 8° C.

In all of our comparative complement-fixation tests conducted with a primary incubation at 38° C. for one hour and a second set at 8° to 10° C. for about eighteen hours, using the same sera, antigens and general technic, we have encountered no evidence indicating the existence of two kinds of antibody, namely, one fixing complement better at 38° C. and a second better at 8° C. When the tests were conducted at 38° C. with one technic and repeated at 8° C. with another technic, differences were encountered and especially with weakly positive sera, but when the same technic was

employed the only differences encountered were positive reactions with some sera tested at 8° C. which reacted negatively at 38° C. and stronger reactions at 8° C. than at 38° C.

In other words a percentage of weakly positive sera and especially those from treated cases of syphilis, will yield negative reactions when tested at 38° C. for one hour and positive reactions when tested at 8° C. for four to eighteen hours. This is especially true if a plain antigen is employed; with cholesterolized extracts the differences are much less, because cholesterolized extracts absorb or fix complement more rapidly at all temperatures and especially at 38° C.

Table I gives a summary of comparative tests employing three different antigens conducted with a primary incubation of one hour at 38° C. and eighteen hours at 8° C. Each serum was heated and used in amount of 0.1 c.c. with an antsheep hemolytic serum. In conducting these tests complement was not titrated, but was used in constant amount of 1 c.c. of a 1:20 dilution; antsheep hemolysin was titrated and used in amount of two units.

TABLE I  
THE INFLUENCE OF PRIMARY INCUBATION UPON COMPLEMENT FIXATION IN  
SYPHILIS WITH DIFFERENT ANTIGENS\*

INCUBATION	SERA TESTED	ANTICOMPLE- MENTARY REACTIONS	PERCENTAGE POSITIVE REACTIONS		
			ANTIGEN I CHOLESTER- OLIZED	ANTIGEN II PLAIN	ACET. INSOL. LIP. ANTIGEN III
Water-bath 1 hour	180	2	82	70	80
Refrigerator 18 hours	180	6	96	89	90

\*Conducted with 0.1 c.c. serum and an antsheep hemolytic system.

The results of these comparative tests may be summarized as follows:

1. In no single instance have we encountered a serum reacting positively at 38° C. and negatively at 8° C.; a fairly large percentage, however, have reacted positively at 8° C. and negatively at 38° C.

2. The tremendous influence of antigen upon the results of these tests is well shown; a cholesterolized extract yielded the highest percentage of positive reactions at both temperatures and while some of these may have been pseudoreactions, we are not sure in a single instance, as all sera were derived from clinic and hospital patients among whom it is difficult to exclude syphilis.



3. All three of the antigens yielded more positive reactions at 8° C. than at 38° C. and especially the plain alcoholic extract of beef heart. The differences in reactions observed after a primary incubation at 38° C. and 8° C. were most marked with the plain extract and least with the cholesterolized extract; the extract of acetone-insoluble lipoids came between these two. These results substantially confirm the observations of Smith and McNeal.

4. There were more anticomplementary reactions at 8° C. than at 38° C. because as shown in a previous article, prolonged incubation at 8° C. results in a greater nonspecific fixation of complement than at 38° C. For this reason *any technic employing the cold method of primary incubation must have the kind and amount of antigen and hemolytic system adjusted accordingly in order to avoid nonspecific reactions.*

5. So far as we can determine *there is but one syphilis antibody in serum and spinal fluid insofar as lipoidal complement fixation is concerned. The differences in reactions observed at 38° C. are ascribed entirely to the influence of temperature upon complement fixation; at 38° C. fixation is more rapid but less complete than occurs at 8° C. and actual destruction of complement is more rapid at 38° C. than at 8° C. rendering prolonged incubation (two hours or more) at 38° C. for the completeness of complement fixation, unsatisfactory in practice because of interference with hemolysis in the controls.*

## Part 2

### A COMPARATIVE STUDY OF METHODS FOR THE PRIMARY INCUBATION

*Technic.*—These experiments were conducted with two different quantitative methods for the purpose of eliciting finer degrees in sensitiveness of complement fixation ascribable to the method of primary incubation.

In the *first method* each serum was used in graded amounts of 0.1 to 0.00016 c.c. with five antigenic units of antigen and two units of guinea pig complement titrated in the presence of each antigen; after the primary incubation one unit of antishoop hemolysin and sheep corpuscles were added and the secondary incubation conducted in a water-bath at 38° C. for one hour, the results being read after the settling of corpuscles.

The results shown in Tables II, III and IV and in Charts 1, 2, 3, 4,



5, 6, 7, 8, and 9 were observed with this technic; in the charts a fixation of 4 represents the maximum, and the curves are plotted accordingly.

In the *second method* a technic modified after the method of Brown-

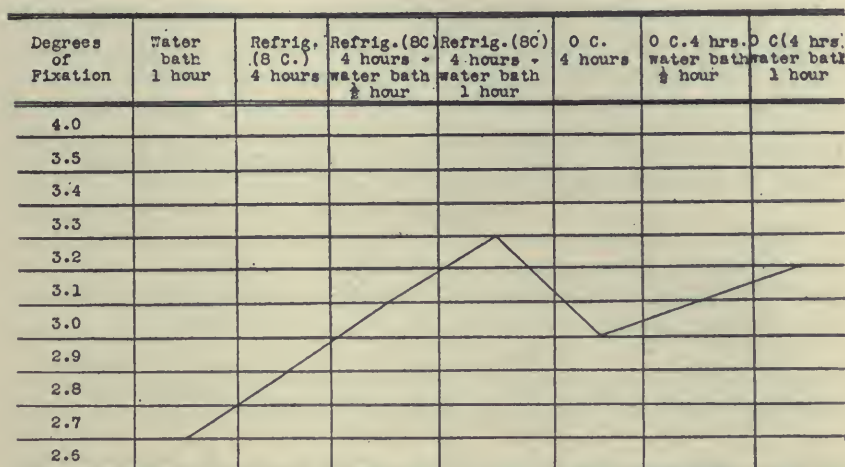


Chart 1.—Influence of primary incubation upon complement-fixation in syphilis. Tests conducted with a 0.2 per cent cholesterolized extract.

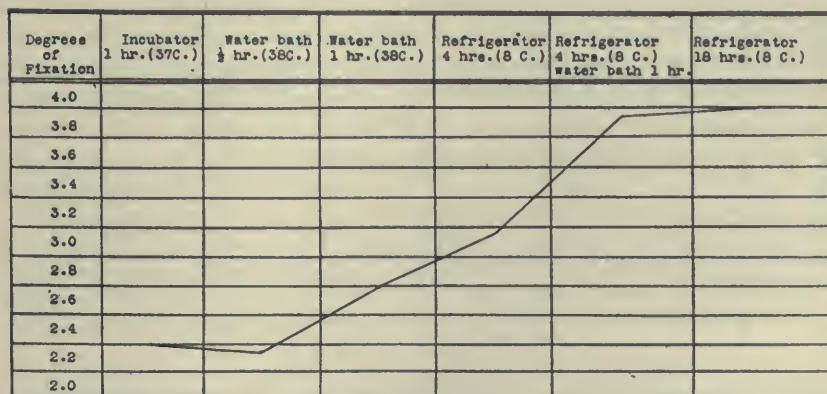


Chart 2.—Influence of kind of primary incubation upon syphilis complement-fixation. Tests conducted with 0.2 per cent cholesterolized extract.

ing and McKenzie, was employed. Each serum was used in constant dose of 0.1 c.c. with two units of complement titrated plain and increasing amounts of complement as 2 to 18 units; the controls on each serum and antigen were set up with 1, 2, 3, 4 and 5 units of comple-

ment. The hemolytic system controls were set up with 1 and 2 units of complement. After the primary incubation one unit of antish sheep hemolysin and sheep corpuscles were added and reincubation con-

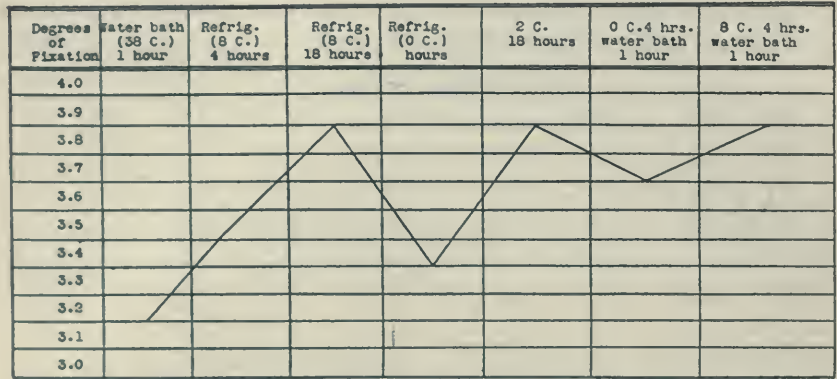


Chart 3.—The influence of temperature upon syphilis complement-fixation with a cholesterolized alcoholic extract of heart muscle.

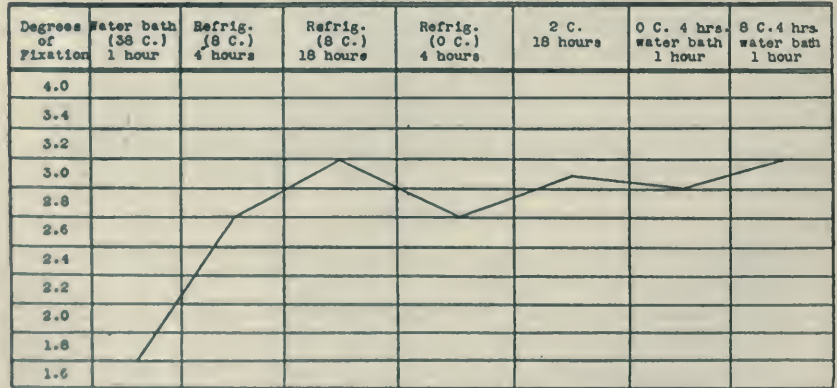


Chart 4.—The influence of temperature upon syphilis complement-fixation with a plain alcoholic extract of heart muscle.

ducted in a water-bath at 38° C. for one hour, the results being read after the settling of corpuscles.

The results of tests with two syphilitic sera and three different antigens are shown in Charts 10, 11, 12, 13, 14 and 15; in preparing these charts the degree of complement fixation is shown according to the units of complement completely or partially fixed; for example, if a reaction was weakly positive with twelve units of complement and

completely negative with thirteen units, the result was recorded as a fixation of twelve units, even though fixation was not complete.

*Results.*—Table II shows the results of tests with thirty syphilitic sera with water-bath and thermostat incubations at 38° C. for fifteen minutes to two hours; as shown in this table fixation occurs somewhat more rapidly in the water-bath and is also somewhat more complete.

In the water-bath the maximum fixation with extracts of acetone-insoluble lipoids may be reached in one hour, although stronger reactions may occur after two hours due largely to destruction of complement; in the thermostat, at least two hours are required for maximum fixation.

TABLE II  
INFLUENCE OF DURATION OF PRIMARY INCUBATION IN THE THERMOSTAT AND WATER-BATH UPON COMPLEMENT FIXATION IN SYPHILIS\*

METHOD OF PRIMARY INCUBATION	NO. OF SYPHILITIC SERA	DURATION IN MINUTES					
		15	30	45	60	90	120
Thermostat; 38° C.	30	17**	17	21	21	24	26
Water-bath; 38° C.	30	19	19	22	29	29	30

\*All tests conducted with an extract of acetone-insoluble lipoids.

\*\*Positive reactions.

*Two hours incubation at 38° C. frequently results in unsatisfactory serum and antigen controls, as this temperature and period enhances nonspecific fixation by serum and antigen alone and also causes actual destruction of complement; for these reasons a primary incubation of two hours cannot be recommended. An incubation of one hour at 38° C., however, is not sufficiently sensitive and for this reason cannot be recommended.*

Table III gives the results of tests with thirty sera with cold incubation varying from one-half to eighteen hours; as shown in this table fixation is surprisingly rapid, but at least eight hours are required for maximum fixation.

TABLE III  
INFLUENCE OF DURATION OF PRIMARY INCUBATION IN THE REFRIGERATOR UPON COMPLEMENT FIXATION IN SYPHILIS\*

METHOD OF PRIMARY INCUBATION	NO. OF SYPHILITIC SERA	DURATION IN HOURS							
		$\frac{1}{2}$	1	$1\frac{1}{2}$	2	3	4	8	18
Refrigerator; 4 to 8° C.	30	21	21	25	26	26	28	30	30

\*All tests conducted with extract of acetone-insoluble lipoids.



As shown in Table IV comparative tests with one hundred and eighteen sera employing an extract of acetone-insoluble lipoids for antigen, have shown that insofar as positive and negative reactions are concerned, the results with one hour in the thermostat, one hour in the water-bath and two hours in a refrigerator were *about* the same; none of these methods, however, is to be recommended, because each is lacking in a sufficient degree of sensitiveness.

TABLE IV  
COMPARATIVE STUDY OF DIFFERENT METHODS OF PRIMARY INCUBATION (118 SERA)

METHODS	RESULTS*			
	POSITIVE	NEGATIVE	STRONGLY** POSITIVE	WEAKLY*** POSITIVE
Incubator; 38° C.; 1 hour	75	43	64	11
Refrigerator; 4-8° C.; 2 hours	74	44	70	4
Water bath; 38° C.; 1 hour	75	43	68	7

\*Tests conducted with an extract of acetone-insoluble lipoids.

\*\*+++ and +++ readings.      \*\*\*++ and + readings.

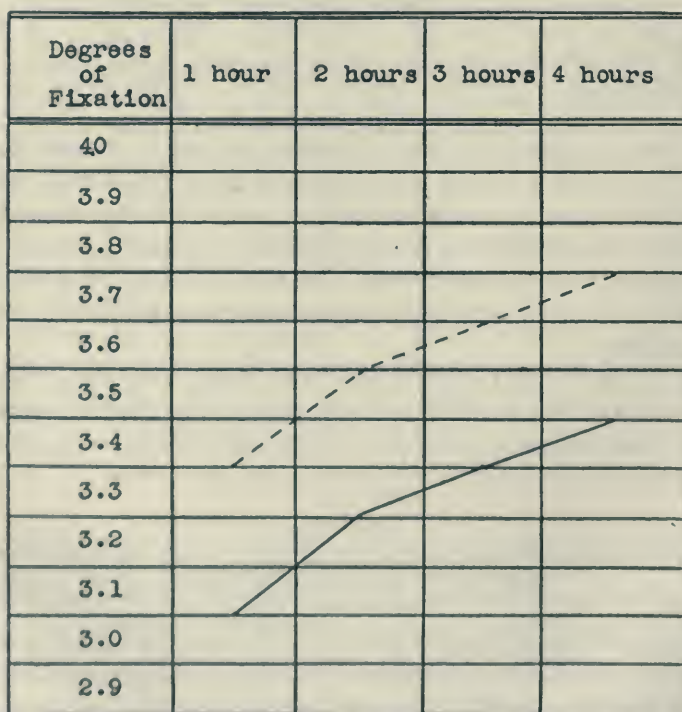


Chart 5.—Curve of complement fixation at 8° C. and 8° C. plus water-bath 38° C.  
 ——— = Fixation at 8° C. (refrigerator).  
 - - - - = Fixation at 8° C. (refrigerator) plus 1 hour water-bath (38° C.)



Chart 1 presents a summary of reactions with twelve sera tested with a cholesterolized extract (0.2 per cent) and seven different primary incubations; Chart 2 presents a summary of reactions with twelve additional sera tested with the same antigen and six different incubations; Charts 3 and 4 present summaries of reactions with eight sera, two different antigens and seven different primary incubations.

Charts 5 and 6 present summaries of reactions with twelve sera tested with a cholesterolized extract (0.2 per cent) and primary incubations at 0° C. for four hours and at 0° C. for four hours plus one

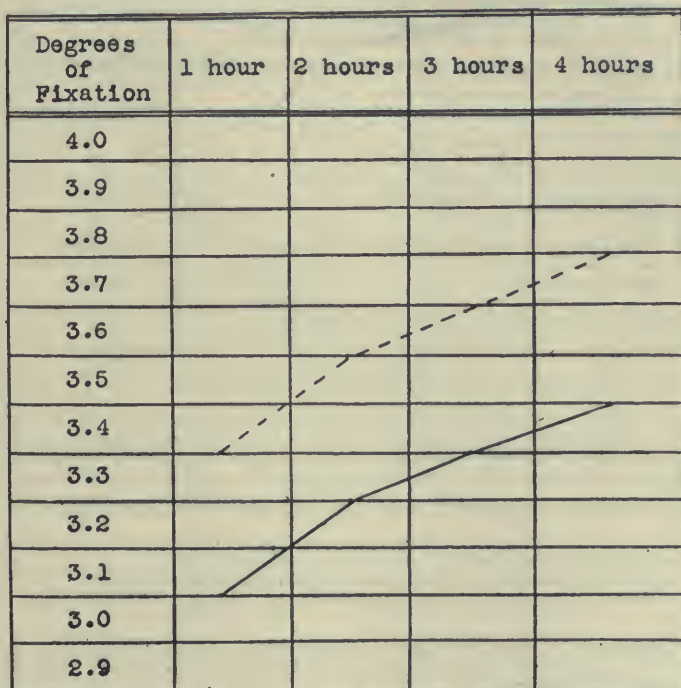


Chart 6.—Curve of complement fixation at 2° C. and 2° C. plus water-bath 38° C.

———— = Fixation in a pan of water and ice (2° C.)

----- = Fixation in a pan of water and ice (2° C.) plus 1 hour in a water-bath at 38° C.

hour at 38° C.; also four hours at 8° C. and four hours at 8° C. plus one hour at 38° C.

Chart 7 presents a summary of reactions with twelve sera tested with four different antigens and nine different primary incubations; Chart 8 presents a summary of reactions with twelve additional sera tested with four different antigens and five different primary incubations.

All of the work summarized in Charts 1 to 8 was conducted with the technic briefly described above under first method; these tests were quantitative with constant amounts of complement and antigen but varying amounts of serum. Chart 9 presents a summary of reactions with twelve sera and a cholesterolized extract (0.2 per cent) with seventeen different kinds of primary incubation; it shows at a glance the relative sensitiveness of reactions with these different incubations.

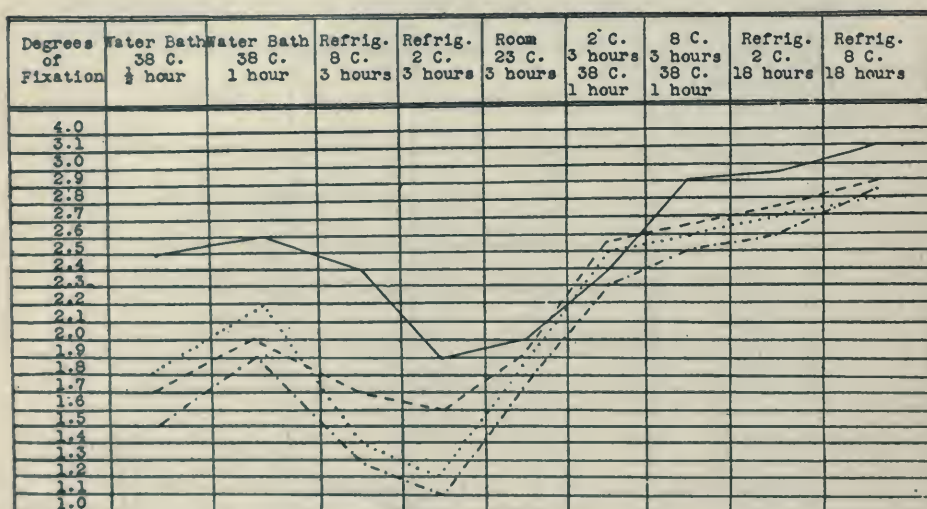


Chart 7.—Influence of temperature upon complement fixation in syphilis with different antigens.

— = curve of fixation with 0.2 per cent cholesterolized extract of beef heart.  
 . . . = curve of fixation with a plain extract of beef heart.  
 - - - = curve of fixation with an extract of acetone-insoluble lipoids.  
 - . - . = curve of fixation with an alcoholic extract of syphilitic liver.

The results are best shown in the tables and charts, but may be summarized as follows:

1. One-half hour in a water-bath is inferior to one hour.
2. One-half hour in a water-bath is frequently, but not always, inferior to one hour in the thermostat; the kind of antigen employed has an important influence.
3. One hour in the water-bath is generally, but not always, superior to one hour in the thermostat.
4. One hour in the water-bath is generally inferior to three hours at 8° to 10° C.

5. Three or four hours at 0° to 2° C. is inferior to three or four hours at 8° to 10° C.

6. Three or four hours at 8° C. plus one hour in the water-bath is superior to one hour in the water-bath and superior to three or four hours at 8° C. alone.

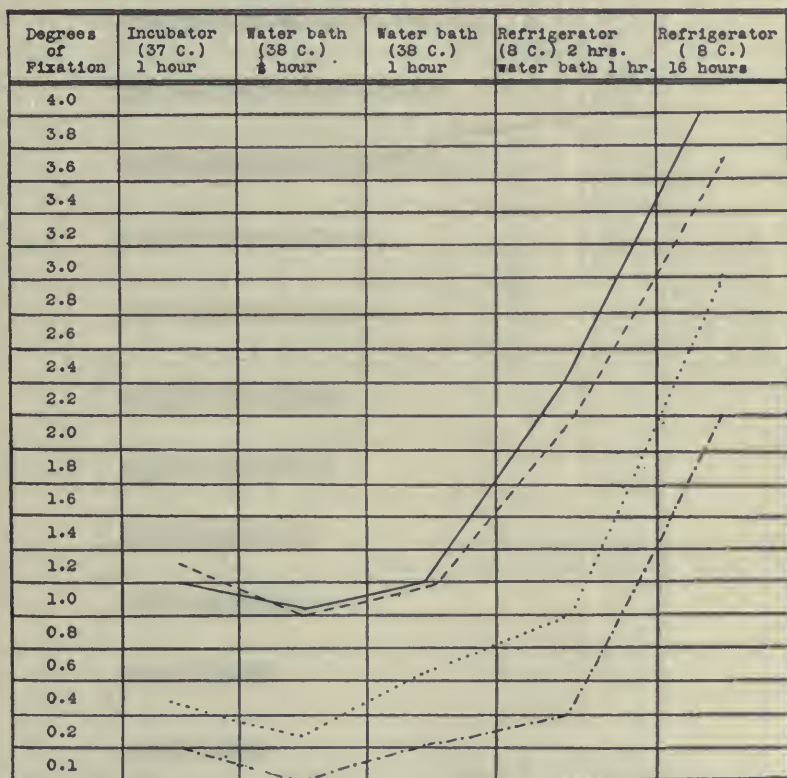


Chart 8.—The influence of temperature upon complement fixation in syphilis with various organ extracts.

- = Fixation with a cholesterolized alcoholic extract of beef heart.
- = Fixation with acetone-insoluble lipoids of beef heart.
- ... = Fixation with a plain alcoholic extract of beef heart.
- . - . = Fixation with a plain alcoholic extract of syphilitic liver.

7. Three hours at 0° to 2° C. plus one hour at 38° C. is inferior to three hours at 8° to 10° C. plus one hour at 38° C.

8. Eighteen hours at 8° C. is slightly superior to three hours at 8° plus one hour at 38° C.

9. Eighteen hours at 8° C. plus one-half to one hour in a water-





bath is the most sensitive of all, but most subject to the objection of nonspecific reactions.

The reactions observed with the second method described above have proved of unusual interest and value as the technic provides

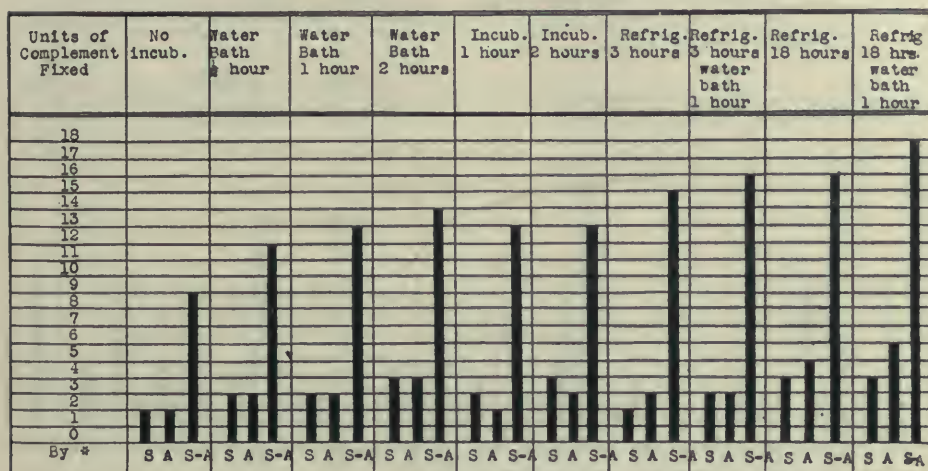


Chart 10.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units by syphilitic serum No. 1 and cholesterolized alcoholic extract of beef heart.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.

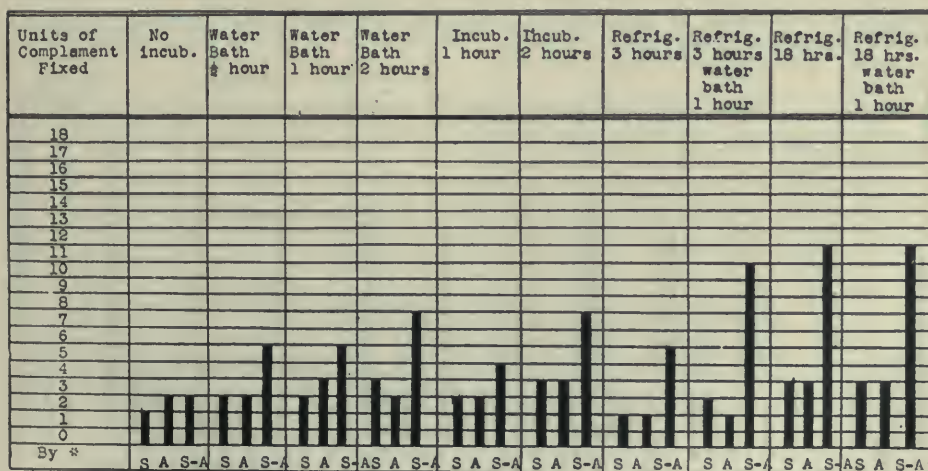


Chart 11.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units, by syphilitic serum No. 1 and a plain alcoholic extract of beef heart.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.

a direct measure of the amount of complement fixed by antigen and serum alone and by mixtures of these, in the ten different kinds of primary incubation.

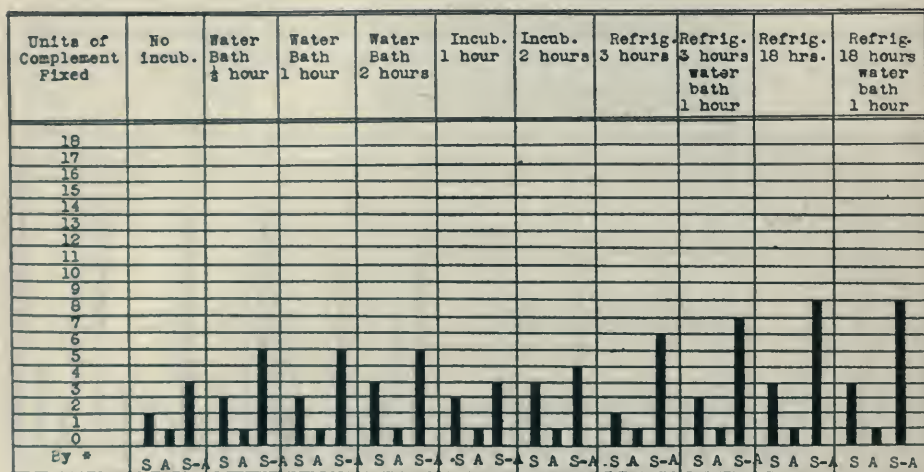


Chart 12.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units, by syphilitic serum No. 1 and an extract of acetone-insoluble lipoids.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.

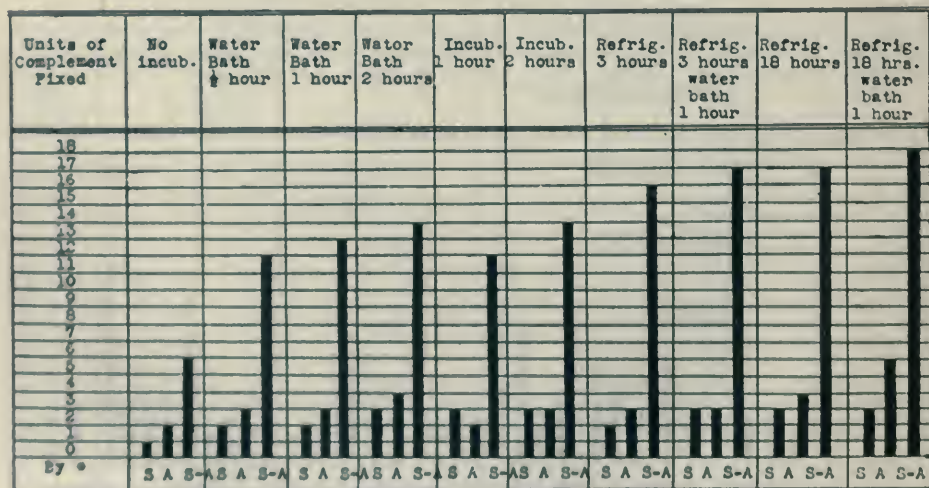


Chart 13.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units, by syphilitic serum No. 2 and a cholesterolized alcoholic extract of beef heart.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.

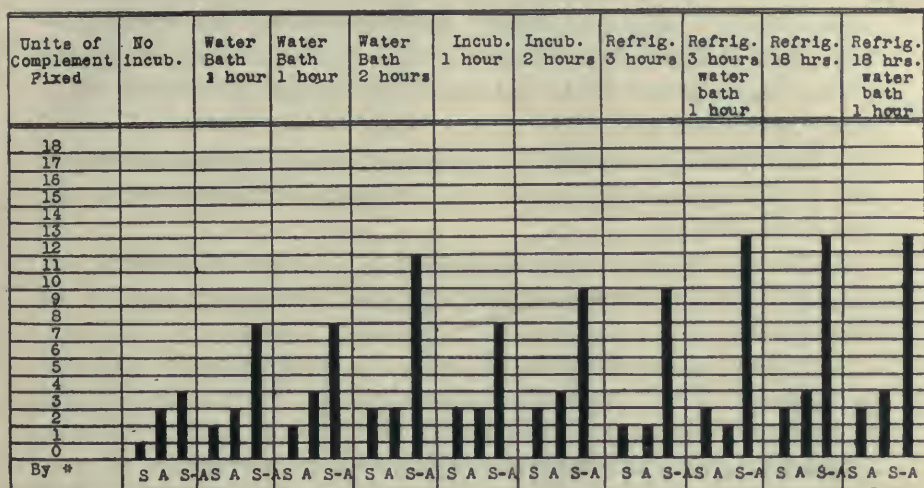


Chart 14.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units, by syphilitic serum No. 2 and a plain alcoholic extract of beef heart.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.

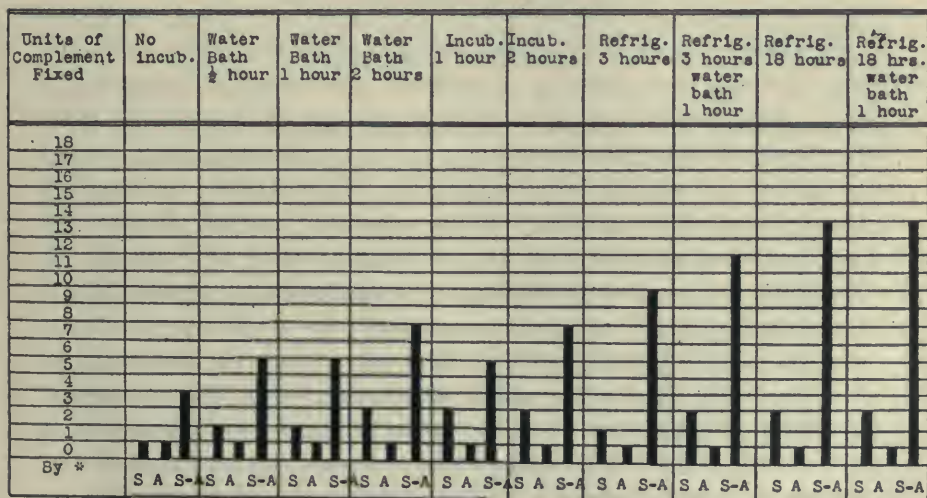


Chart 15.—The influence of temperature and duration of primary incubation upon the fixation of complement measured in units, by syphilitic serum No. 2 and an extract of acetone-insoluble lipoids.

\* S = by serum alone; A = by antigen alone; S-A = by serum and antigen.



Charts 10, 11 and 12 give the results observed with one serum and three different antigens, namely, a cholesterolized and plain alcoholic extract of beef heart and an extract of acetone-insoluble lipoids of beef heart; Charts 13, 14 and 15 give the results of a similar study with a second serum.

1. The results are generally quite similar to those summarized above on the basis of quantitative tests employing each serum in graded amounts.

2. The tremendous influence exerted by the kind of antigen employed is well shown; the cholesterolized extract proved superior in all incubations.

3. The stronger reactions observed in incubations of eighteen hours at 8° C. and incubations of eighteen hours at 8° C. plus one hour at 38° C. are undoubtedly due in part to an increase of nonspecific fixation of complement by serum alone and antigen.

### Part 3

#### PRIMARY INCUBATION RECOMMENDED FOR A STANDARDIZED COMPLEMENT-FIXATION TEST FOR SYPHILIS

Irrespective of the kind of antigen employed, it appears quite certain that the usual periods of primary incubation of one hour at 38° C. in a water-bath or thermostat, do not yield reactions sufficiently sensitive for the serum diagnosis of syphilis employing heated serum and guinea pig complement; the method of choice narrows down to a selection of three or four hours at 8° to 10° C. plus one hour in the water-bath at 38° C. or eighteen hours at 8° to 10° C. The latter is preferred on the basis of somewhat more sensitive reactions but the differences are not marked. *We prefer an incubation of eighteen hours at 8° to 10° C.* for two reasons: (a) the reactions are apparently the most sensitive obtainable within the confines of specificity and (b) the work of testing a large number of sera is facilitated by dividing it into two days instead of crowding it into one, as is necessary with a primary incubation of three hours at 8° C. followed by one hour at 38° C. The differences are not so great however, but that the latter method may be employed if found more convenient; if a refrigerator is not available a temperature of 8° C. is readily secured in an open pan of water and ice for a period of



three hours. A primary incubation of eighteen hours at 8° to 10° C. is best secured in an ordinary ice refrigerator; *the temperature should not be below 6° C. or higher than 10° C. for best results.*

*With either of these kinds of primary incubation it is necessary to select an antigen and hemolytic system which do not result in falsely positive reactions; both of these objects have been worked out satisfactorily and will be considered in following articles.*

#### CONCLUSIONS

1. In comparative complement-fixation tests in syphilis employing the same technic but with one primary incubation in a water-bath at 38° C. for one hour and a second in a refrigerator at 8° C. for four to eighteen hours, there was no evidence of the existence of one antibody fixing complement best at 38° C. and a second reacting best at 8° C. The only differences encountered were positive reactions with some sera tested at 8° C. which reacted negatively at 38° C. and stronger reactions with some sera at 8° C. than at 38° C., especially with plain antigens. No syphilitic sera have been encountered yielding positive complement-fixation reactions with a primary incubation of one hour at 38° C. and negative reactions at 8° C. for four to eighteen hours, provided the same antigen was employed in both.

2. Primary incubation at 8° to 10° C. for four to eighteen hours results in greater fixation or absorption of complement by sera and antigens alone than that occurring during one hour at 38° C. but also results in the specific fixation of more complement by mixtures of serum and antigen; complement fixation is slower but more complete at 8° C. than at 38° C. and especially with plain antigens.

3. Comparative studies in complement fixation in syphilis with two quantitative methods, three different antigens and seventeen different kinds of primary incubation, have shown that the best methods for conducting the primary incubation from the standpoint of sensitiveness of the reactions, are (a) three or four hours at 8° to 10° C. plus one hour in a water-bath at 38° C. and (b) eighteen hours at 8° to 10° C. in a refrigerator. With either of these methods, however, the kind and amount of antigen employed and adjustment of the hemolytic system, are factors of much importance in order to avoid nonspecific reactions.

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## SPECIFIC INHIBITORY REACTION OF CHOLESTERINIZED ANTIGENS IN THE WASSERMANN TEST

BY WILLIAM A. HINTON, M.D., BOSTON, MASS.

*From the Department of Preventive Medicine and Hygiene of the Harvard Medical School, and the Wassermann Laboratory of the Massachusetts Department of Public Health*

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THE choice of a proper antigen for the Wassermann reaction has been a subject for study ever since it was first used in the serologic investigation of syphilis. The various methods of preparing antigens for this test have a common difficulty; namely, that the resulting antigens may have different inhibitory qualities when prepared in an apparently uniform manner from the same kind of tissue. In an ideal Wassermann technic the inhibitory action of the antigen on a suitable hemolytic system should be specific and therefore manifest itself only in the presence of serum or other body fluids of syphilitics. This property is usually called antigenic. I prefer to refer to it as the specific inhibitory reaction and reserve the use of the word antigen for the substance without reference to properties because this part of the Wassermann test does not involve a true antigen-antibody principle.

Serologic rules have been formulated to fix the amount of antigen necessary to give this specific inhibitory reaction. In practice, however, these rules cannot be depended upon solely. This property of the antigen should be determined by laboratory tests and clinical observations on hundreds or better thousands of cases. In such a study every clinical and laboratory method bearing on the diagnosis of syphilis is often necessary to establish or exclude it. The serologic study of a family has often been helpful in obscure cases. The bloods or spinal fluids of a large and varied group of definitely proved syphilitics should constitute the positive controls for testing this most important quality of the antigen, and the blood or fluids from the individuals in whom syphilis is very carefully excluded should be the negative controls.

Cholesterinized antigens are admirably suited for the study of



inhibitory reaction because they often exhibit a wide range of this property. To illustrate this I shall mention two experiences which represent extremes, resulting in false positive reactions in one instance and false negatives in the other. I prepared an antigen consisting of cholesterinized alcoholic extract of beef heart, which gave a positive test in 90 per cent of the specimens from a general medical clinic where the possible incidence of syphilis could not have exceeded 10 or 15 per cent. At another time I used a similarly prepared antigen from human hearts, which if used in one-half or less of its anticomplementary amount would not inhibit the action of complement in the presence of serums obtained from cases of typical secondary syphilis.

From a considerable number of cholesterinized antigens it is possible to select one with a high specific inhibitory reaction with syphilitic serums and fluids and with little or none with nonsyphilitic ones. The source of the heart material for extraction with alcohol is unimportant. Antigens prepared from beef, human, or guinea pig hearts, have shown almost identical qualities. I have used human hearts because they were easy to obtain and usually yield antigens of similar qualitative value. Cholesterinized alcoholic extracts from guinea pig hearts possess the same qualifications, but are usually somewhat more sensitive.

The practice of testing the inhibitory reaction of an antigen by the employment of a single or only four or five specimens of blood from known syphilitics, using a nonsyphilitic serum as a negative control is likely to result in obtaining an excessive number of false positive or false negative reactions. The diverse results obtained by different laboratories on the same specimen are no doubt due largely to inadequately tested antigens. This would also account for the widely different Wassermann statistics on similar groups of individuals by different writers.

The antigens used as a basis for this paper were cholesterinized and gave from 30 to 40 per cent more positive reactions than the most sensitive uncholesterinized ones with which they were compared. For the past seven years I have selected for my tests such cholesterinized antigens as possessed almost identical inhibitory qualities. These cholesterinized antigens have been compared with acetone-insoluble antigens (Noguchi), with plain alcoholic extracts of beef, guinea pig, and human hearts, and also with extracts of

fetal syphilitic livers both aqueous and alcoholic. The comparative tests were made simultaneously with the same reagents exclusive of the antigens. In general a correct comparison of Wassermann methods requires the following conditions:

1. The same reagents must be used in so far as they are common to each of the methods. For example: wrong conclusions might be drawn if the inhibitory qualities of two antigens were tested with complements from two sets of pigs, although the other reagents and test-specimens were the same.

2. A faultless technic must be acquired with a new method or reagent before making critical comparisons. Several years ago I compared the Hecht-Gradwohl technic with mine. More than six weeks' experience was necessary to develop a technic worthy of comparison.

3. A large number of comparative tests must be made. When I compared ice box fixation with that at 37° C., more than 5,000 comparative tests were made before a definite conclusion could be reached. In this comparison, the ice box fixation appeared to give better results in the first 1,000 to 1,500 cases. When, however, the total number of tests had reached about 5,000, a number of specimens having been resubmitted for a second, third, or even fourth test, the different results by the two methods appeared no greater than differences in either.

To illustrate the result of carefully selecting an antigen on the basis of specific inhibitory properties, I have chosen 4,565 cases from more than 150,000 reactions performed during the past five years. These cases represent two socially and intellectually different groups. The first were students in the U. S. Aviation School and were mostly college men. The second upon whom a routine admission Wassermann was made, consisted of inmates of the Massachusetts Reformatory for Women, many of whom are feeble-minded and have either been irregular in their sex relations or are actual prostitutes. These groups are similar only in that they are of about the same ages and practically free from clinical disease except for syphilis and gonorrhea among the women.

From October, 1917, to December, 1918, 3,701 aviation students were examined. A single sample of blood was taken from each man and was tested once only. The specimens of blood were drawn in our laboratory which made it possible to test them in a fresh con-

dition. Each man had passed a rigid physical examination and presented no history or obvious clinical signs of syphilis. Twenty-one cases (0.56 per cent) gave a positive, and 19 (0.5 per cent) gave a doubtful Wassermann reaction. One of the men voluntarily gave me a history of syphilis, explained that the disease had been diagnosed early in the primary stage and stated that prompt treatment had been administered. His reaction was negative. There were probably other cases of this type. Another man denied syphilis but had a typical secondary rash at the time of bleeding. His reaction was positive.

This group shows an extremely low percentage of positive reactions and *demonstrates that the percentage of false positive Wassermann reactions must be very small when carefully tested cholesterinized antigens are used.* If only the secondary syphilitic was actually so infected, which is most unlikely, the total number of positives would be 0.5 per cent. According to my standard, about one-half of the doubtful reactions have positive diagnostic significance. By adding one-half of the doubtful to the positive reactions, the total number of presumably syphilitic would be 0.75 per cent. Although no clinical report was furnished in any of the doubtful or positive cases, it is reasonable to believe that the actual incidence of syphilis in this group at least reaches this figure. No doubt most of these positives could be easily demonstrated as syphilitics after a careful study such as was made in the case of our positive controls.

Three hundred and forty-four (344) inmates of the Reformatory for Women were examined from October, 1917, to December, 1918, the same period during which the aviation students were investigated. Among these 132 (38.3 per cent) were positive and 20 (5.6 per cent) were doubtful. During the past five years the total number of these women was 864 of whom 349 (40 per cent) were positive and 75, (8.6 per cent) were doubtful. All of these figures are based upon their first routine Wassermann test. Table I shows the results obtained from each group.

The percentage of positive reactions among the women differs but slightly during the two periods designated. This indicates that no radical change in methods has occurred during the past five years. In fact neither the inhibiting quality of my antigens nor other elements of my technic have been intentionally changed in seven years.\*

\*Hinton, W. A.: A Standardized Method of Performing the Wassermann Reaction, Am. Jour. Syph., October, 1920, iv, 598.



TABLE I  
RESULTS OF THE WASSERMANN REACTION ON 4,545 CASES

GROUP	POSITIVE WASSERMANN		DOUBTFUL WASSERMANN		NEGATIVE WASSERMANN		TOTALS
	NO.	%	NO.	%	NO.	%	
U. S. Naval Aviation Students Examined from Sept., '17 to Dec., '18	21	.56%	19	.5%	3661	99%	3701
Inmates of Mass. Reform. for Women							
(1) Examined from Sept., 1917, to Dec., 1918	132	38.3%	20	5.6%	192	55.8%	344
(2) Examined from May, 1915, to Mar., 1919 (includes those in 1)	349	40.1%	75	8.6%	438	50.8%	864

In the Reformatory cases the doubtful and negative reactions have added interest as Table II shows.

Seven (0.8 per cent) who had a doubtful and 23 (2.6 per cent) (of the 864 cases) who had a negative reaction were treated luetics. This would suggest that many of the doubtful and a very few of the negative reactions may represent treated syphilitic aviation students. This is a reasonable inference because clinical manifestations rapidly disappear under modern treatment with arsphenamine and mercury.

TABLE II  
FURTHER ANALYSIS OF DOUBTFUL AND NEGATIVE REACTIONS ON REFORMATORY CASES

GROUP	DOUBTFUL WASSERMANN		NEGATIVE WASSERMANN	
	NO.	%	NO.	%
Treated cases of syphilis	7	.8%	23	2.6%
Clinically suspected Syphilitics	6	.7%	23	2.6%

The negative and doubtful reactions among the suspected syphilitic women are also interesting. Only 2.6 per cent of the entire group gave negative reactions and still had some clinical evidence or history of syphilis. The corresponding figures for the suspected doubtfuls is 0.7 per cent. The low percentage of clinically suspected syphilitic women in the negative and doubtful cases is probably too low but appears not far from correct, because most of these women have acquired syphilis during the past ten years and should give positive reactions unless

thoroughly treated according to modern methods. They must have been suspected because of manifest symptoms or previous history of infection—the latter being often difficult to obtain from women. Many of the Reformatory cases were subsequently subjected to repeated tests. Fourteen (14) such cases which were negative on first examination later had positive reactions and all of these cases but two were either persistently positive or had clinical signs or a history of syphilis. Both had two negative reactions and a positive. These fourteen cases make a total of 42 per cent of positive reactions in the entire group of women which is only 2 per cent more than obtained in their first routine examination. This would indicate that a single test in suspected cases has greater significance than usually ascribed.

#### CONCLUSION

When used with a suitably standardized hemolytic system\* carefully selected cholesterinized antigens have a high specific inhibitory reaction and are superior to the plain extracts or artificially prepared lipoids which I have used.

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\*I have purposely refrained from discussing the rôle of the hemolytic system because I have found that antihuman, antichickens and antisheep amboceptor give practically identical results if the same diluted antigen and complement are used for the comparative tests.

## PRIMARY SYPHILIS—EARLY DIAGNOSIS

BY C. GUY LANE, M.D., BOSTON, MASS.

*Assistant Dermatologist, Massachusetts General Hospital; Assistant Physician,  
Department of Dermatology, Boston Dispensary*

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PRIMARY syphilis—preventive medicine—is not the former an essential part of the latter subject, and right at our doors too? Does not early detection and early, persistent, rational treatment of a disease which affects approximately 8 per cent<sup>1</sup> of our population, that is, about 8,000,000 persons in the United States—does not this in itself constitute a public health problem of the first order? Is it not still more important when one considers the insanity from syphilis? We have approximately 200,000 insane in this country, and 12 per cent of this insanity, as a conservative estimate, is caused by syphilis. Williams<sup>2</sup> has estimated that in one state each insane syphilitic costs the state about \$400. If these figures are applied to insanity due to syphilis all over the country, it is found that there is a bill of almost \$10,000,000 for the care of these patients alone, to say nothing of the economic loss which has been caused, and to say nothing of the losses from the more frequent complications of syphilis. Do not these few startling statistics accentuate the necessity for further aggressive measures toward the prevention of such sequelæ? The modern program of attack along this line, in addition to the medical features, lays stress on educational and social measures, and rightly so. In so doing, however, it behooves us as physicians to keep before us the prime necessity for the recognition of the disease in its early stages.

The importance of the syphilitic problem certainly justifies repeated<sup>3</sup> emphasis on the first appearance of a primary infection—yes, on the first suspicion of the appearance of this infection, for it is in this stage, that is, its very earliest and its most localized manifestation, that the most hope can be held out for a really definite, permanent cure, and thus the prevention of possible generalized or late symptoms and the infection of others. It deserves the same emphasis which has been placed in recent years on the early recognition of pulmonary tuberculosis. Many authorities today believe that prompt



and efficient treatment of the disease while still localized at the site of the primary lesion will keep it localized, prevent a generalized infection, and cure the disease, "cure" being used in the absolute sense.

The war served to open the eyes of many people both in the profession and among the laity to venereal diseases as a whole. The government has given added impetus to the movement for their eradication as contagious diseases dangerous to the public health. It has kept the issue a live one. It has provided for the coordination of all efforts in the treatment and control of these diseases. Through recent legislation<sup>4</sup> providing for the Public Health Service it has aided greatly in emphasizing the importance of the subject and has contributed much to the efforts which are being made for their prevention and detection in the early stages and for the proper treatment.

In a recent circular<sup>5</sup> issued by the office of the Surgeon General of the Army are the following statements which can bear repetition: "It is of the highest importance for the cure of syphilis that the initial lesion of syphilis be recognized at the earliest possible moment. To that end: Any excoriation, papule, nodule, crack, 'hair cut,' herpetic or other erosions, no matter how small, as well as ulcers about the genitals—and elsewhere if there is any reason to suspect them—should immediately, *before treatment*, be sent for examination for *Spirochete pallida*. Any lesion which may be a chancre should not be treated with antiseptics, particularly with mercurials, or cauterized chemically or with heat, before examination for spirochete. Chancroids should be suspected of syphilis until repeated examinations for spirochete, repeated Wassermanns, and until sufficient time has elapsed for the failure of the appearance of secondaries to show that syphilitic infection does not exist. No case should be treated for early syphilis until a positive diagnosis is made either by demonstration of the *Spirochete pallida* or by positive Wassermann reaction." The above quotation contains vital information. Read it again. It was issued for the instruction of medical officers during the war, but applies with equal effect to all physicians both military and civil. The above is the sum and substance of the best obtainable information today and should be followed out as closely as possible by every medical man coming in contact with such conditions.

These instructions were issued particularly with reference to lesions on the genitals, but may be applied with equal force to any lesions on other parts, particularly long-standing lesions; indolent lesions that

fail to heal; and apparently sluggish localized infections; lesions that have a satellite, glandular involvement, especially those the cause of which it is often impossible to place. It applies to persistent fissures on the hands, especially about the nails; persistent cold sores on lips or face; obstinate "canker" sores in the mouth; and various other slow-healing, mildly infected areas. Too much emphasis cannot be placed on these instructions. The frequency with which syphilis is found in atypical lesions, and the fact that about 8 per cent<sup>o</sup> of primary lesions are extragenital make it imperative that one consider syphilis in any of these lesions; that we examine each and every one of such lesions as I have described by the latest laboratory methods and not depend wholly on our clinical judgment.

In spite of all our care there will be a few cases develop in which there is no history of a primary lesion, the so-called syphilis d'emblee. Enough cases have been watched from time of exposure to development of secondary symptoms to prove that such may be the case. These, of course, it is impossible for us to get early, but in the cases for which I am making an appeal the consideration of syphilis should be made. In the time of Fournier the best method of certain diagnosis was to wait until the appearance of secondary symptoms before starting treatment. Today, with the scientific measures at our disposal, such advice is almost criminal. Our diagnostic methods are not limited to the appearance of a lesion clinically, as in Fournier's time, for there are at our disposal modern laboratory methods—microscopic with the aid of the dark-field, serologic, and cultural.

Clinical characteristics of lesions are not certain enough today. Not that there are not typical chancres. We do find single, indurated, red or red-brown, painless, dry or abraded papules or nodules, or ulcers, with very slight exudate, and with satellite glands appearing approximately two weeks after exposure, typical so-called Hunterian chancres. These, too, should be checked up with a dark-field examination if possible. In an untreated condition, and with the proper technic, they should always show the *Spirochete pallida*. It is in the borderline cases, or the frankly chancreoid lesions that one is apt to be mistaken. As this bulletin issued by the Surgeon General so well states, in all these cases syphilis should be suspected until repeated examinations, both dark-field and Wassermann, are made. Furthermore, they should be watched and repeated examinations made until



such time as a definite positive or negative finding so far as syphilis is concerned can be made.

Since the discovery of the spirochete by Schaudinn in 1905, and of its easy detection by means of the dark-field, we have had at hand a comparatively sure means of making an early diagnosis. Dark-field examination should reveal the spirochete at almost the earliest appearance of the lesion, and should aid us in making a diagnosis long before the time when the Wassermann usually becomes positive, after two or three weeks, at the time when the infection has become generalized.

In the matter of dark-field examination<sup>7</sup> additional emphasis should be placed on certain statements in the above quotation from the Surgeon General's office, namely, in regard to the local and general treatment of suspected lesions. Treatment with mercury generally, and the local application of caustics or antiseptics, especially mercury, reduces very markedly the possibility of finding the spirochete in the lesion. It may be necessary to stop all treatment for from twenty-four to forty-eight hours and apply normal salt solution locally in order to find the spirochetes. In addition, repeated examinations should be made. It is not enough to form judgment from one smear which is negative.

There are certain difficulties in the technic of dark-field examination which make it advisable to review the essential points in the making of such preparations and their examination. The only equipment needed with an ordinary microscope is a dark-field condenser, and oil immersion lens equipped with a hard rubber "funnel stop," and a source of very bright light, such as is produced by an arc lamp, or the new light-producing apparatus of Bausch and Lomb, and Leitz. With the source of light, preferably in parallel rays, impinging on the mirror and reflected through the dark-field condenser, it is first necessary with the low-power lens to "center" the dark-field stage by the two small adjusting screws on the under side, moving them until the tiny circles on the top of the condenser, as viewed through the microscope, are exactly in the center of the field. Even the dark-field condenser may be dispensed with, for a workable one can be made by pasting a piece of black paper the size of a quarter on the under side of the Abbé condenser.<sup>8</sup>

The lesion itself should be cleaned off with 95 per cent alcohol on gauze, rubbing it as vigorously and squeezing it with as much firmness



as the patient will allow to cause exudation of a small amount of blood-stained serum. If the lesion is covered with epithelium it may be scarified with the point of a scalpel or punctured as described below. This oozing, if mopped off once or twice, will finally result in the appearance on the lesion of almost clear serum. This may be transferred to the cover glass directly by touching the lesion lightly with the cover glass, held in the thumb and forefinger, or transferred by a capillary pipette from the lesion to the cover glass. In placing the slide on the stage of the microscope, it is necessary to be sure that there is oil enough on the top of the dark-field stage to fill the space between the slide and the stage. In addition, in using the oil immersion lens, a drop of oil should be placed on the surface of the cover glass in order that there may be no air space between the lens and the glass. By carefully focusing on the outer edge of the drop, or upon one of the bubbles in the specimen, and adjusting the light, one should be able to see comparatively quickly the vibrating particles, and possibly a blood cell, that denote that one is focused upon the serum. Careful search should be made, not only upon one, but upon several specimens prepared in the same way before rendering a negative report.

It may be possible to obtain material for examination by puncture of the satellite gland, or the indurated base of a suspicious lesion. With sterile hypodermic needle and glass syringe, after the skin over the gland has been painted with iodine, puncture can be made through the capsule of the gland which is held firmly by the thumb and forefinger of one hand. The syringe is gently moved about in an endeavor to macerate a certain limited amount of gland tissue at the point, and suction on the plunger will draw up into the needle a few drops of serum and cells which if examined under the dark-field, may show the characteristic spiral organisms of syphilis. A recent contribution by Schultz<sup>9</sup> suggests the injection of a tiny amount of sterile physiologic sodium chloride solution through the needle into the gland at the point of puncture and the needle rotated a few times more with the idea of making it easier to find the spirochetes.

I have intentionally emphasized details of the dark-field examination because of the importance of this laboratory test in making a definite early diagnosis. The Wassermann test takes second place in this respect, for a positive diagnosis can often be made with a dark-field days before the Wassermann reaction becomes positive. The latter may be positive in seven days, or it may not appear for four or five weeks. Only about 50 or 60 per cent are positive during the

second week.<sup>10</sup> It is not my intention to belittle the value of a Wassermann test or to urge against the advisability of submitting a specimen for a serologic test. On the contrary, I wish to emphasize the importance of the dark-field examination on an early suspicious primary lesion. Again, a negative dark-field and one negative Wassermann report do not necessarily prove that an individual with a suspicious lesion does not have syphilis. Such an individual should have a series of tests at weekly intervals to dispose of the possibility that the serologic reaction has been delayed. Finally, these two laboratory tests should obviate the old method of waiting for secondary symptoms, a method which has already been commented upon as practically a criminal proceeding.

Baerslack<sup>11</sup> suggests the use of culture as a means of early diagnosis in cases in which previous medication prevents diagnosis by dark-field. He removes a piece of tissue from the lesion, or takes a piece of tissue from a freshly excised lesion, and plants this in a tube of horse serum medium which is incubated at 37° C. for from three to five days. This method, of course, is only possible in laboratories equipped with facilities for this sort of work. Keane, of Detroit, describes a variation of this method. He suggests circumcision and growth of the tissue on artificial serum, and finds the spirochetes by dark-field in a day or two. The India ink method, originally suggested by Burri, has been practically supplanted in recent years by the dark-field method.

In the diagnosis by dark-field, it is necessary to call attention to a possible source of error in diagnosis. The *Spirocheta refringens* is occasionally found in smears. This latter organism, however, as compared with the *pallida*, is a shorter, coarser organism with fewer and less regular turns. In the mouth, also, there are several types of spirochetes which may be present, so that a diagnosis of mouth lesions by the dark-field should be made with some hesitation. Great care must be taken to secure a specimen from deeper within the suspected lesion rather than merely from the surface.

Whether another source of error lies in the spirochete-like bodies derived from red blood corpuscles, which have been recently described by Eberson,<sup>12</sup> can be told only by further study.

Before attempting to outline the treatment of early syphilis in detail, I desire to emphasize the words which I have used previously in this article, namely, *prompt* and *efficient*. The patient should be treated as soon as the diagnosis is positively made, not before. It



should be efficient to the point of making sure that the patient is free of syphilis so far as it is humanly possible to determine, not merely that he has one negative Wassermann or that his clinical symptoms disappear. Experience has demonstrated time and again the fallacy of depending on either of these two factors. These tests are not sufficient indication that there will be no recurrence of lesions later on in life. This efficiency in treatment depends on numerous things—kind and amount of drug, method and frequency of use, etc., but the weakest link in the chain is the persistency of treatment. Experience has also taught us the error of giving an individual one or two injections of salvarsan, and the same of mercury, and then considering him cured. It is a serious omission on the part of a physician to fail to impress on the individual the necessity for continuous observation and treatment as prescribed until he can be discharged as cured. The treatment of syphilis today is only as efficient as the means of keeping in touch with our patients, that is, our follow-up system, with reference both to private practice and to institutions. With the aid which the government, through its Public Health Service, and the aid which various states and municipalities are giving, it will continue to be more and more easy to keep in touch with and check up these various early cases which fail to report for treatment at the proper time, and every help should be given to these agencies by both physicians and institutions in order to obviate the appearance of late general manifestations. Again I repeat that treatment is only as efficient as the follow-up system.

Local treatment is of comparatively minor importance. A mild antiseptic wash with calomel ointment or powder is probably as efficient as any. In the general treatment of syphilis there are two generally used methods: first, the method of using arsphenamine once a week for a series of six or eight intravenous injections, along the lines of treatment advocated by the Public Health Service; the second one is the so-called intensive method, with which the name of Politzer<sup>13</sup> of New York in this country is so often associated. The former means the giving of one-tenth gram per 30 pounds body weight of arsphenamine intravenously once a week for six or eight injections. Associated with this is the injection of a soluble mercury salt, bichloride, for instance, one-tenth to one-quarter grain every second day; or an insoluble salt, such as the salicylate, one to two grains intramuscularly every week. A course of soluble salts should consist of from twenty-five to thirty injections, and the insoluble, ten to twelve in-



jections. Details and precautions of this treatment are well given in the instructions issued by the Public Health Service. The intensive method refers to the giving of full doses of arsphenamine every day for three days, followed by injections of mercury by either of the above methods, with a repetition of the arsphenamine in the same way at a later date. This method is based on the theory that it is the closest possible approach to the sterilizing dose first advocated by Ehrlich by providing for a comparatively large amount of the drug in the body at one time. Hazen advises a middle ground, a dose of arsphenamine calculated to the individual, given once in three days for four injections, with four more at weekly intervals. I believe that this accomplishes the same results in the early localized primary cases. Along with this latter scheme, one to two grains of mercury salicylate are given intramuscularly every week for ten to twelve injections. This latter method is the method which was used in my treatment of primary cases while in the army and is the method of choice in early cases at the Boston Dispensary. The cases in whom this treatment is adopted should not show a positive Wassermann at any time. One of these courses, however, is not sufficient. A second, or even a third, course is advised as a matter of precaution against general infection. Standardized forms of treatment have recently been described by Tauber<sup>14</sup> of Cincinnati and Corbus<sup>15</sup> of Chicago.

In the use of neoarsphenamine in place of arsphenamine attention should be paid to the recent remarks of Schamberg<sup>16</sup> stating that an amount of neoarsphenamine approximately twice as great as that of arsphenamine is necessary to produce the same toxic effect on the spirochetes. In whichever method of treatment is adopted it is necessary that emphasis be laid, not so much on salvarsan and mercury, but on salvarsan and mercury for the requisite length of time to clear the individual of every single spirochete, and prevent the appearance of general lesions and destructive manifestations occurring later in life with their inevitable consequences.

#### SUMMARY

Primary syphilis a problem of public health; necessity for early diagnosis; importance of the dark-field examination in all suspicious lesions; dark-field technic; other laboratory methods of early diagnosis; arsphenamine and mercury at earliest possible moment; emphasis on persistent follow-up.

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## CERTAIN FACTORS CONNECTED WITH THE TOXICOLOGICAL TESTING OF ARSPHENAMINE

BY G. C. LAKE, M.D., WASHINGTON, D. C.

*From the Hygienic Laboratory U. S. Public Health Service*

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SOON after the discovery of arsphenamine, Ehrlich realized the necessity of testing the toxicity of this drug on animals before its release, by the manufacturers, for clinical use.

A toxicity test is required because the drug may not be manufactured in chemically pure form, and certain impurities, which cannot be detected by chemical means, may contaminate the final product with a resulting increase in toxicity. With the cutting off of the supply of the German product, it became evident that arsphenamine must be manufactured in this country. The German method of standardization was not known in detail and seemed open to certain objections. Therefore, it was essential to develop a satisfactory method for this purpose.

Preliminary work with this object in view was done in this laboratory by Roth, in 1917, and published in 1918. In this paper Roth reviews the literature on the biological testing of arsphenamine, and neoarsphenamine and reports the results of toxicity tests on both the imported and domestic products, on the basis of which provisional standards were adopted.

The standard for arsphenamine was essentially as follows: The maximal tolerated dose for healthy albino rats shall not be below 50 mg. per kg. body weight, when a 2 per cent, slightly alkaline solution of the drug in freshly glass-distilled water is injected intravenously into the animal at the rate of not more than 0.5 c.c. per minute. For each test, not less than four animals shall be used and at least 75 per cent must survive 48 hours. In the case of neoarsphenamine the specifications were the same except that no alkali is used in preparing the solution, and the dose was placed at 80 mg. per kg. It should be stated that these requirements were placed as low as seemed compatible



with insuring a safe product, so far as this could be determined within the knowledge of the biological test available, rather than with the idea of insuring the highest quality of arspenamine. At this time there was very little of the product available and it was necessary to decide between depriving thousands of patients of the drug, or giving them a preparation which might occasionally produce reactions. Furthermore, no neoarsphenamine appeared on the market until after the standard had been raised to more than double the original figure. Since the beginning of the work these standards have been raised several times, until at present arspenamine is required to pass at 100 mg. per kg. and neoarsphenamine at 200 mg. per kg., in each case requiring the survival of 60 per cent of the animals.\* The raising of the standards was due (1) to an apparent decrease in the toxicity of the products, and (2) to various changes in the treatment of the animals and the technic of carrying out of the tests. It is with these changes, in so far as they relate to arspenamine, that this paper deals. The results are based almost entirely on the observations made in connection with the toxicological testing of this product at the Hygienic Laboratory from December, 1917, to November, 1918, during which time this work was carried out by the writer. The various tables presented in this work show that some lots of arspenamine were apparently much more highly toxic than others. It should be stated that the figures given in many cases are based on results obtained before the introduction of various changes in technic. It is believed, however, that the results given in any one table are comparable in that they were obtained under certain fixed conditions. Some of the products which apparently showed an unusually high toxicity, were later retested according to the official regulations now in force, with the result that they passed the test at a much higher figure.

Some of the variations in technic resulted from experience in our own laboratory, others from conferences with Professor W. J. Gies of Columbia University, and Dr. J. A. Kolmer of the University of Pennsylvania, who were testing these products for the H. A. Metz Laboratories, and the Dermatological Research Laboratories, respectively. It is a pleasure to acknowledge the friendly cooperation shown by these men.

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\*For regulations at present in force for the testing of these products see appendix.

## EXPERIMENTAL PART

## SPECIES OF ANIMAL USED

Roth, 1918, used as experimental animals guinea pigs, rabbits, and albino rats, and of these rats seemed to give more constant results as the maximal tolerated dose was fairly well defined, while with the other animals individual variations were more marked. Another reason for selecting rats was that most of them died or recovered within 48 hours, making results available within a short time. Furthermore, on account of their small size, large numbers of rats can be kept conveniently, an important consideration when a large number of tests have to be made.

## METHOD OF INJECTION

Only the intravenous method has been used in this laboratory, (1) because it was believed that it gave a more uniform rate of absorption than the subcutaneous method as used in Ehrlich's Institute and (2) because it is the method used almost exclusively in the clinical administration of the product.

## INFLUENCE OF THE GENERAL HEALTH OF THE RATS ON TOXICITY

Health and state of nutrition are important factors in the resistance of the animal to arsphenamine. We believe that variations in susceptibility in rats from different colonies or dealers are due solely to differences in the state of health or nutrition of the animals. It requires a great deal of experience in the handling of rats to be able to select those of approximately the same quality. We have not yet worked out a simple practical method by which healthy animals may be selected with any degree of accuracy. As a matter of fact they have usually been taken at random, with the idea that one lot of rats would be of about the same average quality as the next lot. According to the regulations 150 gm. is the maximal weight allowed, which means that all the rats used should *still be in the growing stage*. Probably the best indication that a rat is in good condition, is a regular gain in weight during this growing stage. Animals that remain stationary in weight or show a loss in weight, certainly are not healthy, while those which show a normal gain in weight are probably healthy, and suitable for use, pregnancy being excluded.

The stipulation in the regulations that only healthy rats shall be

TABLE I

## EFFECT OF QUALITY OF RATS ON TOXICITY

The experiments shown in Table I were carried out at a later date than the main part of the work described in this paper. The relative nontoxicity of these lots of drug as compared with that obtained for most lots used throughout the work, is due in part to improvement in the product and in part the changes in technic which have been introduced.

PROD- UCT	NO. OF RAT	SEX	BODY WT. IN GM.	DOSE PER KG. IN MG.	RESULTS * DIED - LIVED	DIED OR DISCHARGED WITHIN	REMARKS
A	A52	F	116	120	*	17 min.	Market rats (Source A) not definitely diseased but infested with lice, and in generally poor condition. Rats A52-A61 and A67-A71 injected from same solution on same date
	A53	F	106	"	-	10 days	
	A54	F	108	"	-	10 days	
	A55	F	109	"	*	35 min.	
	A56	F	104	"	*	3 hr.	
	A57	M	118	100	*	33 min.	
	A58	M	132	"	-	8 days	
	A59	M	101	"	-	8 days	
	A60	M	118	"	*	27 hr.	
	A61	M	121	"	*	73 min.	
	A37	M	97	120	-	11 days	Laboratory stock (Source B) healthy animals
	A38	M	90	"	-	"	
	A39	M	97	"	-	"	
	A40	M	85	"	-	"	
	A41	M	87	"	-	"	
	A67	F	108	120	-	10 days	
	A68	F	118	"	-	"	
	A69	M	137	"	-	"	
	A70	F	138	"	-	"	
	A71	F	122	"	-	"	
B	A122	F	100	100	*	20 hr.	Market rats (Source A) poor quality
	A123	F	102	"	*	20 hr.	
	A124	F	102	"	-	7 days	From same stock as A52-A61
	A125	M	105	"	*	90 min.	
	A126	F	103	"	*	25 min.	
	A127	M	103	100	-	7 days	
	A128	M	112	"	*	1 hr.	
	A129	F	104	"	*	4 hr.	
	A130	F	104	"	-	7 days	
	A131	M	104	"	-	7 days	
	A161	F	119	120	-	8 days	Market rats from source C, appear to be in fairly good condition
	A162	F	102	"	-	8 days	
	A163	F	112	"	*	45 min.	
	A164	F	127	"	-	8 days	
	A165	F	108	"	-	"	
	A166	F	100	120	-	"	
	A167	M	135	"	-	"	
	A168	F	103	"	-	"	
	A169	F	114	"	-	"	
	A170	F	100	"	-	"	



TABLE I—CONT'D

PROD- UCT	NO. OF BAT	SEX	BODY WT. IN GM.	DOSE PER KG. IN MG.	RESULTS * DIED — LIVED	DIED OR DISCHARGED WITHIN	REMARKS
C	A217	F	107	120	*	10 min.	Market rats from Source C being the poorer ones of same lot from which A161-170 were taken
	A218	F	116	"	*	22 hr.	
	A219	M	105	"	*	22 hr.	
	A220	F	103	"	*	1 hr.	
	A221	F	105	"	—	7 days	
	A222	F	133	"	*	35 min.	
	A223	F	100	140	*	15 min.	Laboratory stock (Source B) same quality as A37 etc., above. Rats A217-A227 were injected with same solution on same date
	A224	M	104	"	—	7 days	
	A225	M	118	"	*	22 hr.	
	A226	M	110	"	—	7 days	
	A227	M	109	"	—	7 days	

used is highly important. It cannot be expected that the results obtained in different laboratories will be comparable unless the same quality of rats are used in all the tests. If abnormal or unhealthy animals are used, constant results cannot be obtained even in the same laboratory, for obviously it would be impossible to select rats of the same grade of abnormality.

A few experiments are included (Table I) which strikingly show this difference in susceptibility due to difference in the quality of the rats. Three lots of arsphenamine\* were used and in each case a quantitative difference in toxicity of at least 20 per cent was obtained in results. The difference in quality of the rats used in these experiments was judged from appearances alone. No effort was made to select the best rats from source B, or the worst rats from sources A or C.

In case any doubt exists as to the quality of the rats used, the results should be controlled by putting on parallel tests under identical conditions, using a control number of arsphenamine of which the toxicity has been fairly closely determined. We have reason to believe that in many cases wide apparent differences in toxicity are due to differences in animals used, and not necessarily to differences in the product.

#### THE INFLUENCE OF DIET

Diet is probably an important factor. While we have no definite data to cover this, we believe that animals fed on a well balanced

\*Throughout this paper, any particular lot of arsphenamine is designated by a letter, indicating that it is of a certain make and control number. Firm names are omitted to avoid the danger of erroneous conclusions being reached as to the comparative toxicity of various products, which may or may not be chemically identical.

ration and in a good state of nutrition, will tolerate a higher dose, and will react more uniformly, the latter being by far the more important consideration from the standpoint of standardization of a test.

#### THE EFFECT OF A FULL STOMACH ON TOXICITY

Early in the course of testing market preparations, it became evident that animals which were used while their stomachs were gorged with food were more susceptible to the drug. The explanation was that the animals received an excessive dose due to the added weight of the food in the stomach. Furthermore, a full digestive tract in itself may increase the unfavorable action of arspenamine. It has been recommended for several years that in the clinical administration of the drug, care should be taken to instruct the patient to take little or no food for the several hours preceding, and following its administration. It was found that a 100 gm. rat frequently increased in weight 10 per cent or more after feeding. For this reason the provision was placed in the regulations that rats should not have access to any food for 12 to 18 hours before being injected. Even after this period of fasting some food usually remains in the stomach.

#### IMPORTANCE OF PROPER CARE OF THE ANIMALS

The animals should be cared for preferably by an attendant who is familiar with their habits, who will handle them with the utmost gentleness, keep the cages clean, feed and water them absolutely according to instructions, and who can attend to these duties regularly. It has been our experience that something usually goes wrong when the man assigned to this duty is on leave and the work is turned over to some one else, not because the other man is inefficient, but because it requires a considerable amount of experience, as well as a certain knack to raise rats successfully, and to keep them in a healthy condition.

TABLE II

THE TIME AT WHICH DEATHS OCCURRED (1141 RATS INJECTED)

MORTALITY		DEATHS WITHIN 1ST HR.		DEATHS FROM 1-24 HR.		DEATHS WITHIN 24-48 HR.		DEATHS WITHIN 48 HR. TO 15 DAYS	
325	28.5%	102	31.38%	174	53.54%	13	4%	36	11.08%

Conclusions: 89 per cent of all deaths occurred within the 48-hour period.

## PERIOD OF OBSERVATION NECESSARY

Table II showing the time of death of 325 rats, in a series of 1141 injected, in making the routine tests up to August 1, 1918, indicates that the 48 hour observation period required in the official test is sufficient for practical use and is not apt to lead to any great error. The deaths occurring within less than 24 hours, many of them within the first hour, amounted to 85 per cent; the total number within 48 hours to 89 per cent, the remaining 11 per cent being scattered from the third to fifteenth days. In many cases the dose given was so low that no deaths occurred, while in some cases it was so high that most of the animals died. However, there had not been, up to this time, any very definite relationship between the size of the dose and the time after the injection at which death occurred. Sudden deaths had occurred occasionally after the administration of relatively low doses. With the improvement in technic, based on the results to be given in the succeeding pages, these sudden deaths have been largely eliminated and now occur only occasionally and then as a rule, where the dose is near the minimal lethal one.

## INFLUENCE OF THE PROPER HOLDING OF THE ANIMALS DURING INJECTION

Up to September, 1918, the method used in the Hygienic Laboratory for holding rats during the intravenous injection of arsphenamine was such as permitted small but vigorous movements, though those of large excursion were eliminated.

On visiting the laboratories of Dr. Kolmer and Professor Gies we noticed that their rats, which were secured to the board by means of small cords attached to each leg by a slip knot, struggled very little and in fact did not seem to be much disturbed by the injection. We were so impressed by the advantage of the method that we decided to try it in our own work, for in addition to the advantage of being able to inject the animal by the most humane method possible, it seemed reasonable from the physiologic standpoint that some of the sudden deaths might be eliminated. Animals which die soon after intravenous injection of arsphenamine usually show numerous fine hemorrhages in some or all of the organs, apparently sufficient to have caused death. If a large dose is given at a time when the circulation is greatly disturbed by the animal's efforts to free itself, the chances for sudden deaths are probably much higher than when the circulation is as nearly normal as possible at the time of injection.



TABLE III

EFFECT ON TOXICITY OF PROPER HOLDING OF THE ANIMALS DURING THE INJECTION  
(80 MG. PER KG. DOSAGE THROUGHOUT)

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	RATS HELD BY OLDER METHOD	RESULT * DIED - LIVED	DIED OR DISCHARGED WITHIN
N	2619	M	175	Yes	*	1 hour
	2620	M	142	"	*	4 hours
	2621	M	141	"	*	20 hours
	2622	M	130	"	*	50 minutes
	2623	F	115	"	*	20 minutes
	2629	M	115	"	*	2 hours
	2630	F	115	"	*	6 minutes
	2631	F	104	"	*	8 hours
	2632	M	104	"	*	10 minutes
	2633	M	124	"	*	2 hours
	2794	M	150	"	*	20 minutes
	2795	M	145	"	*	15 minutes
	2796	F	127	No	-	Dis. 8 days
	2797	M	109	"	-	" " "
	2798	F	114	"	-	" " "
	2809	M	144	"	*	15 minutes
	2810	M	140	"	-	8 days
	2811	M	113	"	-	8 days
	2812	M	125	"	-	8 days
	2813	F	100	"	-	8 days
O	2624	M	117	Yes	*	11 minutes
	2625	M	125	"	*	24 hours
	2626	M	137	"	*	7 minutes
	2627	F	145	"	*	24 hours
	2628	M	110	"	*	1 hour
	2634	M	109	"	*	4 hours
	2635	M	110	"	*	5 days
	2636	F	105	"	*	7 minutes
	2637	F	105	"	-	9 days
	2638	F	102	"	*	20 minutes
	2799	M	137	No	-	8 days
	2800	M	119	"	-	8 days
	2801	M	142	"	-	8 days
	2802	M	110	"	-	8 days
	2803	M	125	"	-	8 days
P	2589	M	195	Yes	-	8 days
	2590	M	184	"	*	3 minutes
	2591	M	127	"	*	4 minutes
	2592	M	124	"	*	20 minutes
	2593	M	119	"	*	12 minutes
	2594	F	101	"	-	8 days
	2595	M	121	"	*	12 hours
	2596	M	109	"	*	2 hours
	2597	M	137	"	*	9 hours
	2598	M	110	"	*	10 minutes
	2599	M	175	"	*	8 minutes

Of 42 rats injected, of those held by older method, 34 died within 24 hours.  
Of 18 rats injected by use of new method, 3 died within 24 hours.

TABLE III—Continued

EFFECT ON TOXICITY OF PROPER HOLDING OF THE ANIMALS DURING THE INJECTION  
(80 MG. PER KG. DOSAGE THROUGHOUT)

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	RATS HELD BY OLDER METHOD	RESULT * DIED — LIVED	DIED OR DISCHARGED WITHIN
	2600	M	132	Yes	—	8 days
	2601	M	119	"	—	8 days
	2602	M	114	"	*	14 minutes
	2603	M	142	"	*	10 minutes
	2789	M	145	"	*	7 minutes
	2790	M	137	"	—	8 days
	2791	M	175	"	*	3 hours
	2792	M	136	"	*	11 minutes
	2793	M	160	"	—	8 days
	2804	F	115	No	—	8 days
	2805	F	119	"	—	8 days
	2806	M	117	"	—	8 days
	2807	M	137	"	*	5 hours
	2808	F	122	"	—	8 days

Of 42 rats injected, of those held by older method, 34 died within 24 hours.

Of 18 rats injected by use of new method, 3 died within 24 hours.

The comparative results obtained when the rats were held by the older and the later method are shown in Table III. Of 42 rats injected, when held by the older procedure, 34 died within 24 hours (most of them within a few minutes), while of 18 rats injected by the newer process only three died within this period, one within 15 minutes, the other two after several hours. Three lots of arsphenamine were used, the same dose being employed throughout.

These results indicate that the method employed in holding the animals, which causes the least nervous irritation and physical exertion during the administration of the drug has an important influence on lowering its apparent toxicity. Since changing our technic in this respect, not only has the apparent toxicity been lowered, but the number of deaths occurring within a few minutes after the injection has decreased to a marked extent.

#### THE EFFECT OF PREGNANCY ON RESULTS

Soon after the testing of market preparations for toxicity was begun, it became quite noticeable that pregnant animals frequently died soon after the administration of a dose which was well tolerated by the other rats used in the test. Such animals had been used unin-

tentionally, the condition being discovered at necropsy. Therefore it seemed advisable to carry out some experiments to settle this point definitely.

Two groups of rats were selected for this purpose (see Table IV).

TABLE IV  
THE INFLUENCE OF PREGNANCY ON RESULTS  
PRODUCT D  
(Dose, 60 mg. per kg. throughout.)

NO. OF ANIMAL	SEX	WT. IN GM.	RESULT * DEAD - LIVING	DIED OR DISCHARGED WITHIN	REMARKS
1053	F	182	*	2 hrs.	Pregnant
1054	F	134	*	7 hrs.	Acute enteritis
1055	F	174	*	2 hrs.	Pregnant
1056	F	155	*	2.5 hrs.	Pregnant
1069	F	176	*	3 hrs.	Pregnant
1070	F	150	-	12 days	Seems normal
1071	F	169	*	3.5 hrs.	Pregnant
1072	F	185	*	3.5 hrs.	Pregnant
1085	M	115	*	3 hrs.	
1086	M	137	-	12 days	
1087	M	115	-	12 days	
1088	M	127	-	12 days	
1089	M	112	-	12 days	
1090	M	103	-	12 days	
1091	M	117	*	6 days	
1092	M	115	*	20 hrs.	
1105	F	135	*	10 min.	All heavily pregnant embryos -9-20% body weight.
1106	F	137	*	8 min.	
1107	F	155	*	15 min.	
1108	F	179	*	4 hrs.	
1109	M	145	-	8 days	
1110	M	145	-	8 days	
1111	M	165	*	4 days	
1112	M	175	-	8 days	

NOTE.—Amount of alkali used in preparation of above solutions—1.5 c.c. N/√1 NaOH per 200 mg. of drug.

The first group, including rats numbered up to No. 1092 inclusive, consisted of eight females, most of which from appearances alone, did not seem to be pregnant but which were suspected to be, on account of their age and weight, and eight males to serve as controls. The second group consisted of four females which appeared to be in a fairly advanced stage of pregnancy, and four male controls. All animals received the same dose in mg. of the drug per kg. of weight. Seven of



the eight females in Group 1 died within 7 hours. In some of them pregnancy was not far advanced. Only two of the controls died within 20 hours or less. All of the females in Group 2 died within four hours or less, and on necropsy were found pregnant, the uterus weighing from 9 to 20 per cent of the body weight. Only one of the controls died and that on the fourth day.

These experiments show that pregnant female rats are much more susceptible to arsphenamine than males when the drug is given in proportion to body weight. The control animals should have been nonpregnant females rather than males. However, in the several thousand rats used so far we have had no reason to believe that there is any great difference in susceptibility between males and nonpregnant females.

In the case of albino rats the pregnant uterus may constitute as much as 25 per cent of the entire body weight of the animal. It is obvious that if such an animal receives a dose based on body weight, the maternal blood will contain a relatively larger amount of the drug than that of a nonpregnant animal of the same weight. There is also the possibility that pregnancy *per se* affects susceptibility in some degree, although we have no data on this point.

The importance of making a postmortem examination on every animal that dies is emphasized by the above results, and in case pregnancy appears to have influenced the result the test should be repeated. It is difficult to determine pregnancy in a rat from the appearance of the animal alone, unless the condition is moderately advanced. The complication may, however, be eliminated to a large extent by using females, between 100 and 120 gm. in weight. We have occasionally found pregnancy even in a 100 gm. rat, while in those weighing from 120 up the condition is quite common. The most satisfactory method for avoiding this difficulty consists in separating the females from the males, when they have reached a weight of 80 to 90 gm.

#### INDIVIDUAL SUSCEPTIBILITY

No matter how uniform the stock of rats, or how carefully they are selected, it is impossible to secure uniformity of results within narrow limits, without using a considerable number of animals with the same dose. It is not uncommon to have one rat die or occasionally two, of a group of five, with a given dosage and on repeating the test to have all live. To overcome this irregularity and still keep the

number of animals to be used in a test within reasonable limits, provision is made in the official regulations that a test may be put on a lot of five animals, and repeated if necessary, the final results being based on the percentage of the total number of animals surviving. Furthermore, the standard is placed sufficiently high to allow for deaths of the more susceptible animals, even with a good product. On account of the considerable difference in individual susceptibility, it seems preferable to arbitrarily define the maximal tolerated dose, as the dose which allows a majority of the animals to survive, rather than one which allows all to survive.

#### THE EFFECT ON TOXICITY OF HEATING ACID SOLUTIONS IN NARROW GLASS-STOPPERED CYLINDERS

It seemed important to determine the effect of heat on solutions of arspenamine, (1) because some preparations are readily soluble only in hot water and (2) because hot water has been used by many clinicians in making solutions of various preparations, where there was no necessity for doing so and in disregard of definite instructions to the contrary.

Our attention has been called to instances where there has been difficulty in making a solution by shaking the drug with hot water in glass-stoppered cylinders, and the cylinders have been placed in boiling water for some time in order to complete the solution. We have also learned that it is not an uncommon practice to add the drug to water boiling freely over the flame, and allow it to boil until all the gelatinous masses which occasionally form, are dissolved.

The experiments here recorded (Table V) were for the purpose of determining whether any material increase in toxicity resulted from heating the drug in the acid solution, with as little exposure to the air as possible, for a short period. It was intended that the amount of heating should correspond roughly to about the amount which might be used occasionally in the preparation of solutions for clinical use.

Two control numbers of arspenamine were used. The solutions were made up in tall, narrow glass-stoppered cylinders by two methods (1) as recommended by the manufacturer, one in water boiling hot, the other in cold water and (2) after being prepared in this way, the solutions were then heated in a specially arranged water-bath at boiling temperature for from five to sixteen minutes,

TABLE V

THE EFFECT OF HEATING ACID SOLUTIONS, IN NARROW GLASS-STOPPERED CYLINDERS,  
ON TOXICITY.

NOTE.—Each group of animals as indicated by the heavy lines, constitutes a separate experiment in which the rats were injected with solutions made from the same ampoule and, with one exception, injected within the same hour.

A.—Results obtained with Product Q: Solutions made (1) with hot water, and (2) with hot water and then heated as indicated in table. Alkalinization after cooling. Dosage same throughout.

NO. OF RAT	SEX	WT. IN GM.	TIME HEATED TO 100° C.	RESULT * DIED - LIVED	DIED OR DISCHARGED WITHIN
3120	F	106	—	—	8 days
3121	M	118	—	*	8 days
3122	M	101	—	—	8 days
3123	M	98	—	—	8 days
3135	M	100	5 min.	*	15 min.
3136	F	98	"	—	8 days
3137	M	100	"	—	8 days
3138	F	100	"	*	1 hr.
3139	M	101	"	*	1 hr.
3156	F	111	—	*	1 hr.
3157	M	136	—	*	17 hr.
3158	M	106	—	—	7 days
3159	F	121	—	—	"
3160	M	101	—	—	"
3161	F	118	10 min.†	—	"
3162	F	99	"	—	"
3163	M	106	"	—	"
3164	M	117	"	—	"
3165	M	128	"	*	16 hr.
3171	M	110	—	—	9 days
3172	M	110	—	—	"
3173	F	109	—	—	"
3174	F	105	—	*	2 hr.
3175	F	118	—	—	9 days
3166	F	115	10 min.	*	3 hr.
3167	M	108	"	*	5 hr.
3168	M	106	"	*	4 hr.
3169	M	135	"	*	20 hr.
3170	M	160	"	*	6 days
3186	M	135	—	—	9 days
3187	M	122	—	—	"
3188	M	132	—	—	"
3189	M	98	—	—	"
3190	F	108	—	—	"
3191	F	98	16 min.	*	30 min.
3192	M	102	"	*	9 days
3193	F	117	"	*	18 min.
3194	M	124	"	—	9 days
3195	M	99	"	—	"

† The only explanation suggested for the discrepancy of results with this group is that the apparatus was not working properly, and the usual amount of heat was not employed.



TABLE V—Continued

NO. OF RAT	SEX	WT. IN GM.	TIME HEATED TO 100° C.	RESULT * DIED — LIVED	DIED OR DISCHARGED WITHIN
3206	M	106	—	—	8 days
3207	M	118	—	—	8 days
3208	F	132	—	—	8 days
3209	M	101	—	—	8 days
3210	M	109	—	—	8 days
3211	M	139	10 min.	*	4 hr.
3212	M	125	"	*	1.5 hr.
3213	M	125	"	*	4 hr.
3214	M	134	"	*	1.5 hr.
3215	M	106	"	*	10 min.
3216	F	119	—	—	8 days
3217	M	101	—	—	8 days
3218	M	118	—	—	8 days
3219	M	106	—	*	1 day
3220	M	118	—	*	1 day
3221	M	105	10 min.	*	8 days
3222	M	150	"	*	45 min.
3223	M	131	"	*	40 min.
3224	M	100	"	*	24 hr.
3225	F	109	"	*	35 min.
3341	M	95	—	—	9 days
3342	M	98	—	*	2 days
3343	F	96	—	*	9 days
3344	M	97	—	*	9 days
3345	F	96	—	*	9 days
3346	M	90	10 min.	*	2 days
3347	F	100	"	*	1 hr.
3348	F	92	"	*	5 hr.
3349	M	91	"	*	5 hr.
3350	F	97	"	—	9 days
3351	F	96	"	—	9 days
3352	F	97	"	—	9 days
3353	M	97	"	*	12 min.
3354	M	96	"	*	8 min.
3355	F	94	"	*	1 hr.

B.—Results obtained with Product F: Solutions made (1) with cold water, and (2) with cold water and then heated as indicated in table. Alkalinization after cooling. Dosage same throughout.

3146	F	100	—	*	45 min.
3147	M	98	—	—	7 days
3148	F	100	—	—	7 days
3149	F	96	—	—	7 days
3150	M	104	—	—	7 days
3151	M	136	5 min.	*	1 hr.
3152	F	97	"	—	7 days
3153	M	105	"	*	30 min.
3154	F	99	"	—	7 days
3155	F	97	"	*	30 min.
3176	M	144	—	—	9 days
3177	F	124	—	—	9 days

TABLE V—Continued

NO. OF RAT	SEX	WT. IN GM.	TIME HEATED TO 100° C.	RESULT * DIED - LIVED	DIED OR DISCHARGED WITHIN
3178	M	118	—	*	1 hr.
3179	F	106	—	—	9 days
3180	F	107	—	—	9 days
3181	F	109	10 min.	—	9 days
3182	F	132	"	*	1 hr.
3183	M	122	"	*	1 hr.
3184	M	99	"	—	9 days
3185	F	107	"	*	1 hr.
3226	M	110	—	*	7 days
3227	M	129	—	—	8 days
3228	M	117	—	—	8 days
3229	M	136	—	—	8 days
3230	M	113	—	—	8 days
3231	M	94	10 min.	*	45 min.
3232	M	106	"	—	8 days
3233	M	100	"	*	36 min.
3234	M	127	"	*	24 hr.
3235	M	131	"	—	8 days
3301	F	115	—	—	10 days
3303	F	94	—	*	3.5 hr.
3303	F	94	—	—	10 days
3304	F	109	—	—	10 days
3305	M	128	—	—	10 days
3306	M	104	10 min.	*	2 hr.
3307	M	95	"	*	5 hr.
3308	M	102	"	*	7 min.
3309	F	112	"	*	7 min.
3310	M	122	"	*	1 hr.
3311	F	103	—	*	3.5 hr.
3312	F	94	—	—	10 days
3313	M	94	—	—	10 days
3314	F	95	—	—	10 days
3315	M	97	—	—	10 days
3316	F	114	10 min.	*	50 min.
3317	F	92	"	*	34 min.
3318	M	90	"	*	6 hr.
3319	F	95	"	*	28 min.
3320	M	90	"	*	30 min.
3376	M	102	—	—	8 days
3377	M	124	—	—	8 days
3378	M	108	—	*	11 min.
3379	M	154	—	—	8 days
3380	F	116	—	—	8 days
3381	F	116	10 min.	*	4 min.
3382	M	112	"	—	8 days
3383	M	120	"	—	8 days
3384	M	129	"	*	17 hr.
3385	M	114	"	—	8 days

SUMMARY OF TABLE V

PRODUCT	SOLUTION MADE WITH	NO. OF ANIMALS USED	DEATHS RESULTING WITHIN 48 HOURS
Q	Hot water	34	17%
Q	Hot water and held at 100° C. 5 to 16 min.	40	65%
F	Cold water	30	17%
F	Cold water and held at 100° C. 5 to 10 min.	30	70%

usually for ten minutes. After cooling the solutions, the alkali was added and testing for toxicity carried out in the usual manner. The same lot numbers and the same doses of each product were used in all the experiments.

Briefly summarized, the product designated as "Q" made into solution according to Method 1 caused death, in less than 48 hours, of 17 per cent of the animals, whereas when treated according to Method 2, it caused the death of 65 per cent. Product designated as "F" gave a similar result; made up in cold water it caused the death of 17 per cent of the animals, while after heating, it caused the death of 70 per cent.

While the results obtained show that there is a marked increase in toxicity due to heating, even when in an acid solution, they do not indicate how much this difference might amount to, expressed as mg. per kg., nor at what rate the toxicity increases in relation to the time the heating is prolonged.

It is a matter of common knowledge, chemically, that arspheamine in solution decomposes even at low temperatures, especially when exposed to the air. The decomposition is caused by a chemical reaction. The velocity of all chemical reactions is increased by raising the temperature; consequently hot solutions of arspheamine always decompose more rapidly than cold solutions. It has been held that the decomposition products of arspheamine are more toxic than the original substance. The results obtained are therefore in harmony with chemical considerations.

We have no experimental data on the point, but it is believed from theoretical considerations that heating the alkalized solution increases the toxicity of the product, even more than heating the acid



solution. While we have not learned of solutions for clinical use being heated after the addition of the alkali, we do know that alkali has frequently been added to a hot solution. We believe that if hot water must be used in preparing a solution, the solution should be thoroughly cooled before adding the alkali.

THE EFFECT ON TOXICITY OF PREPARING SOLUTIONS IN WIDE MOUTHED  
ERLENMEYER FLASKS, WITH THE AID OF HEAT

During the earlier part of 1918 in the routine testing of arsphenamine, solutions were, for a time, made up as follows: Into a 200 to 300 c.c. Erlenmeyer flask, 10 to 15 c.c. of boiling hot distilled water was introduced, and then 400 mg. of the drug sprinkled on the surface. With the aid of a little shaking the solution was, as a rule, easily made. The water was sometimes allowed to boil over a small flame while the powder was being added and the solution being made. The solution was then transferred to a graduated glass-stoppered cylinder, and the flask rinsed with small amounts of distilled water. After cooling, the required amount of alkali was added and the solution made up to volume.

While this procedure enables one to prepare the solutions easily it has the disadvantage (1) that heat is used and (2) that on account of the broad surface exposed and the scant depth of the water, conditions for oxidation are excellent. Heating the drug under these conditions probably causes a more rapid decomposition than heating it in the tall closed cylinders in the manner referred to above. The increase in toxicity resulting from the preparation of a solution as just outlined is shown by the following experiments.

Of the 20 rats injected with the same, (see Table VI) 13, or 65 per cent, died within less than 16 hours, while of 24 rats used in control experiments where the solution was made with cold water 3, or 12.5 per cent died within 24 hours. The same lot and dose of arsphenamine was used in all the tests.

These results indicate that the practice of making solutions by sprinkling the drug on the surface of hot or boiling water should be condemned. Probably the increase in toxicity would not be great if the volume of water used were large and if it were quickly cooled as soon as the solutions were made. The danger lies in the assumption that the heating is not likely to increase the toxicity and that in many instances it will be unduly heated or actually boiled. There is also

TABLE VI  
THE EFFECT OF PREPARING SOLUTIONS IN WIDE-MOUTHED ERLLENMEYER FLASKS  
WITH THE AID OF HEAT ON TOXICITY. (Product E, Dosage 60 mg. per kg.)

NO. OF RAT	SEX	WT. IN GM.	RESULTS * DIED - LIVED	REMARKS
<i>A. Solutions made up with heat.</i>				
781	F	112	*	6 hr.
782	F	109	*	2 hr.
783	F	107	*	16 hr.
784	F	104	*	2 hr.
785	F	104	*	2 hr.
786	M	101	*	2 hr.
787	F	100	-	14 days
788	M	106	-	14 days
1057	M	178	*	2 hr.
1058	M	164	*	5 hr.
1059	M	127	-	12 days
1060	M	152	-	12 days
1061	M	162	-	2 days
1063	M	144	*	12 days
1064	M	135	*	40 min.
1081	M	115	*	30 min.
1082	F	129	*	5 hr.
1083	M	163	*	4 hr.
1084	M	142	*	3 hr.
1062	M	149	-	12 days
<i>B. Control Experiments. Solutions made up in cold water.</i>				
945	F	105	-	15 days
946	M	148	-	15 days
947	M	118	*	24 hr.
948	F	154	*	4 days
949	M	128	-	15 days
950	M	127	*	9 days
951	M	170	-	15 days
952	M	117	-	15 days
1037	F	131	-	13 days
1038	F	135	-	13 days
1039	F	120	-	13 days
1040	F	110	-	13 days
1041	F	137	-	13 days
1042	F	141	-	13 days
1043	M	125	-	13 days
1044	M	125	-	13 days
1077	M	167	-	13 days
1078	M	155	*	2 hr.
1079	M	146	*	4 hr.
1080	M	167	-	12 days
1109	M	175	-	8 days
1110	M	145	-	8 days
1111	M	165	-	8 days
1112	M	145	*	4 days

## CONCLUSIONS OF TABLE VI.

1. Out of 20 rats injected with solution prepared by heating, 13 died within less than 24 hours.

2. Out of 24 rats injected with solution prepared with cold water, 18 lived through observations period, only 3 died in 24 hours.

NOTE.—Amount of alkali used in preparation of solutions=1.5 c.c. n/1 NaOH per 200 mg. of drug.

the possibility that some products will stand a considerable amount of heating without increasing their toxicity to a marked degree, while others having slightly different physical or chemical characteristics will not stand this procedure. The directions of the manufacturer should always be carefully followed. Failure to do so may properly place the responsibility for an unfavorable result on the operator and not on the product.

In the next section of this paper there is suggested a method whereby relatively insoluble preparations of arsphenamine may be dissolved quite readily without the use of hot water.

#### THE INFLUENCE OF ETHYL ALCOHOL, FOR INCREASING THE SOLUBILITY OF POORLY SOLUBLE PRODUCTS, ON TOXICITY

Our attention was first called to the use of ethyl alcohol in the preparation of arsphenamine for intravenous injection in July, 1918, in connection with making toxicity tests on an imported product. In the descriptive circular accompanying this product it was recommended that 1 c.c. of ethyl alcohol be used to moisten the drug before attempting to dissolve it in water. This procedure enabled us to prepare quickly a clear solution of this product, which was not readily soluble in water alone. As one of the American products at that time resembled this imported product in appearance and solubility, it seemed worth while to determine whether alcohol affected the solubility of the former in the same way. This was done with promising results.

There is nothing new about this procedure. Mr. Feruta, Director of the Sankyo Laboratories, while visiting the Hygienic Laboratory in September, 1918, informed us that it had been used for a long time and that he considered the use of a small amount of alcohol, in preparing the solution, good technic. When Ehrlich and his associates first produced "Salvarsan" they found it necessary to treat it with methyl alcohol in order to make the solution most readily. Later, they solved the problem of making a product readily soluble in water, so that there was no longer any need for preliminary treatment by other agents for increasing its solubility.

The following experiments (Table VII) show that this use of ethyl alcohol lowers the toxicity appreciably, as compared with that



of solutions made up in the shortest possible time with hot water. Furthermore, it eliminates the danger of solutions being rendered unduly toxic by *overheating*. (See comparison of the effect of heating solutions for ten minutes at 100° C. as compared with that of solutions made up in the shortest possible time in hot water.) Finally, it is a much more convenient and rapid method of making the solution of a product which is not readily soluble in water at room temperature.

The alcohol appears to increase the solubility of the product, not by dissolving it, but by penetrating throughout and moistening the dry arspenamine. When water is added and the container quickly shaken, no gelatinous masses form as is the case when water alone is used, these masses being the principal cause of delay in making solutions.

TABLE VII

THE EFFECT ON TOXICITY OF PREPARING SOLUTIONS IN COLD WATER, BY AID OF ALCOHOL

I. Results with Product R

A. Ethyl alcohol 90%, 0.5 to 1 c.c. used to moisten 200 mg. drug before adding water

NO. OF RAT	SEX	WT. IN GM.	DOSE PER KILO MGM.	RATE OF INJECTION SEC.	RESULT * DEAD - LIVING	DIED OR DISCHARGED WITHIN:
1701	F	95	80	60	-	10 days
1702	M	139	80	60	-	10 days
1704	M	100	80	42	-	10 days
1774	M	105	80	52	*	49 min.
1775	M	101	80	35	-	12 days
1776	M	102	80	52	-	12 days

B. Solutions made with hot water as usual.

1601	M	117	80	70	-	13 days
1602	M	135	80	50	*	50 min.
1603	M	130	80	55	*	17 hr.
1604	M	132	80	44	*	15 min.
1765	M	85	80	40	*	30 min.
1766	M	90	80	40	*	7 min.
1767	M	85	80	40	*	3 hr.
1768	M	101	80	52	*	25 hr.
1769	M	102	70	55	-	12 days
1770	M	122	70	55	*	36 min.
1771	M	136	70	60	*	2.5 hr.
1772	M	100	70	45	-	12 days
1817	M	150	70	60	*	4 hr.
1818	M	115	70	50	-	11 days
1819	M	115	70	45	*	2 hr.
1820	M	101	70	42	-	11 days

TABLE VII—CONT'D  
II. Results with Product Q

A. Ethyl alcohol, abs. 0.5 c.c. used to moisten 200 mg. drug before adding water

NO. OF RAT	SEX	WT. IN GM.	DOSE PER KILO MGM.	RATE OF INJECTION SEC.	RESULT * DEAD — LIVING	DIED OR DISCHARGED WITHIN :
3406	M	120	120	75	—	12 days
3407	F	95	120	78	—	12 days
3408	F	94	120	65	—	12 days
3409	F	114	120	81	—	12 days
3410	F	96	120	50	—	12 days
3411	F	114	120	75	—	12 days
3412	F	103	120	68	—	12 days
3413	M	100	120	73	—	12 days
3414	F	96	120	57	—	12 days
3415	M	118	120	75	—	12 days
3586	M	115	120	82	*	2 days
3587	M	107	120	74	—	7 days
3588	F	102	120	64	*	24 hr.
3589	M	97	120	65	—	7 days
3590	M	118	120	78	*	24 hr.
3616	M	95	120	63	*	24 hr.
3617	F	105	120	71	—	9 days
3618	F	94	120	67	—	9 days
3619	M	91	120	70	—	9 days
3620	F	102	120	67	—	9 days
3651	F	99	120	98	*	18 hr.
3652	F	101	120	73	*	18 hr.
3653	F	96	120	72	*	50 min.
3654	F	117	120	95	—	8 days
3655	M	112	120	103	—	8 days
3656	M	76	140	75	—	8 days
3657	F	96	140	73	*	25 min.
3658	F	77	140	72	*	18 hr.
3659	M	90	140	75	*	20 min.
3660	F	97	140	75	—	8 days

B. Solutions made with hot water as usual

3591	M	120	120	75	•	7 days
3592	F	111	120	80	•	24 hr.
3593	M	101	120	61	—	7 days
3594	M	142	120	98	—	7 days
3595	M	166	120	113	—	7 days
3611	M	117	120	75	*	24 hr.
3612	M	107	120	70	—	9 days
3613	M	94	120	70	•	9 days
3614	F	93	120	59	*	40 hr.
3615	M	90	120	70	—	9 days
3641	F	101	140	90	•	40 min.
3642	F	94	140	60	•	6 days
3643	F	100	140	84	—	8 days
3644	F	97	140	85	•	18 hr.
3645	M	91	140	84	•	8 days
3646	M	108	140	97	•	18 hr.
3647	F	92	140	80	•	50 min.
3648	F	94	140	73	—	8 days
3649	F	95	140	70	•	3 days
3650	F	96	140	82	•	3 days

THE EFFECT OF USING DIFFERENT AMOUNTS OF SODIUM HYDRATE IN  
PREPARING SOLUTIONS

Danysz, 1917, concluded, on the basis of theoretical considerations and a number of experiments, that arspenamine solutions made up with an excess of alkali were less toxic than those prepared in the usual manner. He made solutions of "Luargol," which he considers essentially an antimony silver salt of the arspenamine base differing from arspenamine in its action only in minor details, as follows: Sodium hydroxide was added in amount sufficient (1) to form the monosodium salt (2) to form a salt midway between the monosodium and disodium salts, (3) to form the disodium salt and (4)  $\frac{1}{2}$  mol. of sodium hydroxide in excess of that necessary to form the disodium salt. [The amount used in the second solution represents about the amount used, or perhaps a little more, in the preparation of solutions for clinical use by many physicians.] Danysz found that when he injected these solutions intravenously into rabbits at the same rate, Solution 1 was twice as toxic as 2, and that 3 and 4 were less toxic than either of these. The hyperalkaline solution (4) caused pain on being injected and in some cases a subsequent obstruction and atrophy of the veins injected.

A considerable number of tests were made at the Hygienic Laboratory during the summer of 1918, to determine whether or not similar results could be obtained on albino rats. Two per cent solutions were made up (1) with 1.5 c.c. N/1 NaOH per 200 mg. of the drug, the amount which was being used in the routine testing, and (2) with 2.5 c.c. N/1 NaOH, which is 30 per cent in excess of the amount necessary to form the disodium salt.

The results obtained are given in Table VIII. They show that a definite decrease in toxicity results from the use of excess alkali, which with some lots of the drug amounts to 20 mg. per kg. or more, while with other lots there is no marked difference. However, in no instance did the preparation containing the excess alkali appear more toxic than the other one. Furthermore the number of deaths occurring in less than 24 hours and in from 24 to 48 hours, was somewhat higher when the smaller amount of alkali was used, while the number of deaths occurring after 48 hours was greater in case of the hyperalkaline solution (see Table IX).

The general conclusions seem warranted, therefore, that solutions containing an amount of alkali in excess of that necessary to form the



TABLE VIII  
THE INFLUENCE OF THE AMOUNT OF ALKALI USED IN PREPARING SOLUTIONS, ON  
TOXICITY

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	AMT. N/1 NaOH PER 200 MG. DRUG	DOSE PER KG. IN MG.	RESULT * DIED -- LIVED
S	1441	M	140	1.5 c.c.	100	—
	1442	M	105	"	"	*
	1443	M	147	"	"	—
	1444	M	132	"	"	—
	1273	M	118	2.5 c.c.	120	—
	1274	M	130	"	"	—
	1275	M	130	"	"	—
	1276	M	160	"	"	—
	1437	M	142	"	140	*
	1438	M	140	"	"	*
	1439	M	104	"	"	*
	1440	M	142	"	"	*
T	1177	M	130	1.5 c.c.	120	—
	1178	M	118	"	"	—
	1179	F	112	"	"	—
	1180	M	127	"	"	*
	1193	F	117	1.4 c.c.	140	*
	1194	F	112	"	"	—
	1195	F	135	"	"	*
	1196	F	112	"	"	*
	1301	M	125	1.6 c.c.	"	*
	1302	M	142	"	"	*
	1303	M	127	"	"	—
	1304	M	120	"	"	—
	1473	M	126	2.5 c.c.	"	*
	1474	M	118	"	"	*
	1475	M	124	"	"	*
	1476	M	119	"	"	—
	1297	M	122	"	160	*
	1298	M	132	"	"	*
U	1299	M	130	"	"	*
	1300	M	124	"	"	*
	1469	M	120	1.5 c.c.	100	—
	1470	M	102	"	"	—
	1471	M	117	"	"	—
	1472	M	111	"	"	—
	1429	M	134	"	120	*
	1430	M	145	"	"	*
	1431	M	135	"	"	—
	1432	M	132	"	"	*
V	1433	M	159	2.5 c.c.	140	*
	1434	M	151	"	"	—
	1435	M	142	"	"	—
	1436	M	117	2.5 c.c.	140	—
	1401	M	100	"	150	*
	1402	M	128	"	"	*
	1404	M	141	"	"	*
	1365	M	132	1.6 c.c.	120	—
	1366	M	101	"	"	*
	1367	M	103	"	140	—
	1368	M	112	"	"	—

TABLE VIII—Continued

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	AMT. N/1 NaOH PER 200 MG. DRUG	DOSE PER KG. IN MG.	RESULT * DIED — LIVED
V	1789	F	106	1.6 c.c.	140	*
	1790	F	105	"	"	*
	1791	F	106	"	"	*
	1792	F	97	"	"	—
	1413	M	112	1.5 c.c.	150	*
	1414	M	122	"	"	—
	1415	M	144	"	"	*
	1416	M	98	"	"	*
	1793	M	119	2.5 c.c.	140	*
	1794	M	115	"	"	—
	1795	M	100	"	"	—
	1796	M	125	"	"	*
	1425	M	127	"	160	*
	1426	M	124	"	"	—
	1427	M	147	"	"	*
	1428	M	107	"	"	*
W	1371	M	145	1.6 c.c.	140	—
	1372	M	115	"	"	—
	1797	M	96	"	"	—
	1798	M	134	"	"	—
	1799	M	114	"	"	—
	1800	M	95	"	"	—
	1417	M	140	"	160	*
	1418	M	141	"	"	*
	1419	M	147	"	"	—
	1420	M	125	"	"	*
	1801	F	121	2.5 c.c.	140	—
	1802	F	102	"	"	—
	1803	F	101	"	"	—
	1804	F	100	"	"	*
	1421	M	122	"	160	*
	1422	M	116	"	"	—
X	1423	M	122	"	"	*
	1424	M	142	"	"	*
	1361	F	107	1.6 c.c.	140	*
	1362	F	100	"	"	—
	1363	F	102	"	120	*
	1364	F	117	"	"	—
	1777	M	125	1.5 c.c.	130	—
	1778	M	115	"	"	—
	1779	M	95	1.5 c.c.	130	—
	1780	M	120	"	"	—
	1409	M	128	"	150	*
	1410	M	108	"	"	*
	1411	M	118	"	"	*
	1412	M	112	"	"	*
	1489	M	189	2.5 c.c.	"	—
	1490	M	96	"	"	—
	1491	M	118	"	"	—
	1492	M	109	"	"	—
	1781	M	115	"	160	—
	1782	F	114	"	"	*
	1783	M	115	"	"	—
	1784	F	108	"	"	—

TABLE VIII—Continued

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	AMT. N/1 NaOH PER 200 MG. DRUG	DOSE PER KG. IN MG.	RESULT * DIED — LIVED
D	1757	F	115	1.5 c.c.	70	*
	1758	F	80	"	"	—
	1759	F	103	"	"	—
	1760	M	109	"	"	—
	1189	F	110	1.3 c.c.	80	*
	1190	F	112	"†	"	*
	1191	F	109	"	"	*
	1192	F	119	"	"	*
	1761	M	85	2.5 c.c.	70	—
	1762	M	98	"	"	*
	1763	M	120	"	"	—
	1764	M	115	"	"	—
	1265	M	157	"	80	—
	1266	M	149	"	"	*
	1267	M	170	"	"	*
	1268	M	185	"	"	*
G	1197	F	127	1.4 c.c.	70	—
	1198	F	123	"	"	—
	1199	F	130	"	"	—
	1200	F	130	"	"	—
	1213	F	112	"	80	*
	1214	F	117	"	"	*
	1215	F	114	"	"	—
	1216	F	117	"	"	*
	1285	M	152	2.5 c.c.	"	—
	1286	M	146	"	"	—
	1287	M	100	"	"	—
	1288	M	133	"	"	—
	1277	M	182	"	100	*
	1278	M	132	"	"	*
	1279	M	98	"	"	*
	1280	M	122	"	"	*
H	1201	F	102	1.4 c.c.	70	—
	1202	F	104	"	"	—
	1203	F	129	"	"	—
	1204	F	117	"	"	—
	1217	F	120	"	80	*
	1218	F	132	"	"	*
	1219	F	107	"	"	*
	1220	F	112	"	"	*
	1785	F	105	2.5 c.c.	"	—
	1786	F	120	"	"	—
	1787	F	100	"	"	—
	1788	F	105	"	"	—
	1283	M	162	"	100	—
	1284	M	153	"	"	—
	1513	M	112	"	"	*
	1514	M	110	"	"	—
	1515	M	114	"	"	*
	1516	M	110	"	"	*
	1281	M	142	"	120	*
	1282	M	150	"	"	—

† The relatively smaller amount of alkali used in this experiment may account in part for the sudden deaths.



TABLE VIII—Continued

PRODUCT	NO. OF RAT	SEX	WT. IN GM.	AMT. N/1 NaOH PER 200 MG. DRUG	DOSE PER KG. IN MG.	RESULT * DIED — LIVED
I	1289	M	137	1.4 c.c.	80	—
	1290	M	129	"	"	*
	1291	M	124	"	"	—
	1292	M	124	"	"	—
	1293	M	124	"	100	—
	1294	M	102	"	"	*
	1309	M	165	"	"	—
	1306	M	140	"	120	*
	1307	M	128	"	"	*
	1308	M	123	"	"	*
	1333	M	149	2.5 c.c.	"	*
	1334	M	132	"	"	—
	1335	M	138	"	"	*
	1336	M	137	"	"	*
	1517	M	126	"	140	*
	1518	M	110	"	"	*
	1519	M	102	"	"	*
	1520	M	105	"	"	*

NOTE.—The differences in results with various lots of the drug make it appear that either chemical differences may be present in the control numbers or that the method is inaccurate, or that both explanations are partly right.

disodium salt, exhibit a lower toxicity and a decrease in the number of sudden or "accidental deaths," of the experimental animals as compared with solutions containing only enough alkali to form a mixture of the monosodium and disodium salts.

Partly on the basis of this work but more on account of the results shown by tabulated reports on thousands of clinical administrations from stations of the Public Health Service, which showed that there was an extremely wide variation in the amount of alkali being used, it was suggested that a definite amount of normal sodium hydroxide solution should be used in the preparation of the drug for intravenous injection. The amount specified was 0.9 c.c. normal NaOH to each 0.1 gram of the arspenamine. This figure was selected as representing approximately the amount necessary to form the disodium salt. [The exact amount is 0.84 c.c.] Before this action was taken a number of tests were made on rats which showed that this amount of alkali gave results comparable to those obtained with the higher amount used in the above experiments. Therefore, 0.9 c.c. NaOH per 0.1 gram of drug was adopted in the routine testing.

TABLE IX  
(SUPPLEMENTARY TO TABLE VIII)

SHOWING THE TIME AT WHICH DEATH OCCURRED (ALL LOTS HAVING 100 PER CENT SURVIVALS OR DEATHS BEING ELIMINATED) AFTER INJECTION OF SOLUTION MADE ALKALINE WITH SODIUM HYDRATE IN AMOUNTS:

SUFFICIENT (1) TO FORM A SALT BETWEEN THE MONO-SODIUM AND DISODIUM SALTS				(2) IN EXCESS OF THAT NECESSARY TO FORM THE DISODIUM SALT	
	No.	%		No.	%
Deaths in less than 24 hours	21	38.2		19	36.54
Deaths in 24 to 48 hours	4	7.27		2	3.84
Deaths after 48 hours	3	5.45		8	15.38
Survivals	27	49.1		23	44.23

Conclusions: The hyperalkaline solution appears (1) to be on the average about 10 per cent less toxic and (2) to cause fewer early deaths, and a greater number of later deaths, which perhaps more correctly represent the true toxic effect of the drug.

In connection with the experiments for determining the effect on toxicity of different amounts of alkali in arsphenamine solutions, it seemed advisable to make control experiments to show the effect of the intravenous administration of various amounts and dilutions of NaOH alone, having a higher concentration of the free alkali than any dose of the alkalized solution of the arsphenamine contained of total alkali. (See Table X.)

TABLE X  
THE TOXICITY OF SODIUM HYDRATE

RAT NO.	SEX	WT. IN GM.	CONCENTRATIONS OF NaOH	DOSE IN MG. PER KG.	RESULT + DIED - LIVED	REMARKS
1883	M	139	1 c.c. = 7 mg.	56	- 13 days	used rats
1884	M	130	"	"	- "	" "
1885	M	150	"	"	- "	" "
1886	M	120	"	"	- "	" "
1887	M	106	1 c.c. = 10 mg.	80	- "	" "
1888	M	125	"	"	- "	" "
1889	M	159	"	"	- "	" "
1890	M	115	"	"	- "	" "
1895	M	137	"	100	- "	" "
1896	M	140	"	"	- "	" "
1897	M	140	"	"	- "	" "
1898	M	119	"	"	- "	" "
1899	M	115	1 c.c. = 12 mg.	96	- "	" "
1900	M	157	"	"	- "	" "
1901	M	135	"	"	- "	" "
1902	M	120	"	"	- "	" "
1891	F	156	1 c.c. = 20 mg.	93	+ 2 min.	convulsions
1892	M	137	"	90	- 13 days	"
1893	M	126	"	55	+ 2 min.	"
1894	M	130	"	130	- 13 days	"

As a matter of convenience and to make conditions as comparable as possible, the solutions of alkali were made by adding amounts of N/1 NaOH varying from 1.75 c.c. to 5 c.c., to distilled water and in each case making the total volume up to 10 c.c.

The experiments show that sodium hydrate (2.5 c.c. N/1 in 10 c.c.) when given in a dose of 100 mg. per kg. causes no apparent harm although it contains nearly six times as much NaOH as would be given with a 100 mg. per kg. dose of arsphenamine in the routine testing (0.9 c.c. N/1 for 100 mg. of drug).

When given in higher concentration, 3 c.c. N/1 NaOH in 10 c.c., but in somewhat smaller volume, the total amount of alkali injected being nearly the same, similar results were obtained. When a N/2 NaOH solution was injected slowly and in small amount, convulsions occurred before nearly as much NaOH had been introduced as in the experiments just referred to. If the injections were promptly stopped, on the occurrence of convulsions the animals recovered after a time, otherwise they died almost at once.

The results show that the symptoms and deaths solely attributable to the alkali, are dependent on the absolute amount of alkali injected in a unit of time, and occur only when considerable amounts of alkali are injected.

#### THE EFFECT ON TOXICITY OF THE RATE OF INJECTION AND THE CONCENTRATION OF THE SOLUTION

These two factors are so closely related that they should be considered together. The rate of injection may be varied, while the concentration of the solution remains constant, or the concentration varied while the rate remains constant, so that the same amount of drug is mixed with the blood stream in the same length of time. Within reasonable limits either factor can be varied and a similar effect produced with the same amount of drug.

The concentration of the drug used in our experiments, with few exceptions was 2 per cent. This concentration was selected (1) because any dose that would ordinarily be used could be conveniently given with a 1 c.c. syringe (graduated to 0.01 c.c.), and (2) because it was thought that the larger volumes necessary with more dilute solutions might disturb the circulation too much. These reasons, however, do not seem well founded, as we have found (1) that rats may be readily injected by the gravity method, with any dilution



TABLE XI  
THE INFLUENCE OF RATE OF INJECTION ON TOXICITY

PROD- UCT	NO. OF RAT	SEX	WT. IN GM.	DOSE IN MG. PER KG.	TIME OF INJECTION IN SEC.	RESULT *DIED - LIVED	REMARKS
K	397	F	102	60	35	-	rel. rapid injec.
	398	F	107	"	32	-	" " "
	399	F	106	"	35	*	" " "
	400	F	112	"	40	*	" " "
	817	M	105	"	65	-	rel. slow injec.
	818	F	125	"	60	-	" " "
	819	M	131	"	70	-	" " "
	820	F	138	"	85	-	" " "
L	741	F	109	50	32	-	rel. rapid injec.
	742	M	100	"	33	*	" " "
	743	F	104	"	33	*	" " "
	744	F	115	"	33	*	" " "
	721	M	112	60	55	*	" " "
	722	M	129	"	30	-	" " "
	723	F	110	"	35	*	" " "
	724	M	110	"	37	*	" " "
	789	F	101	"	60	*	rel. slow injec.
	790	F	108	"	68	-	" " "
	791	F	119	"	73	-	" " "
M	792	M	115	"	72	-	" " "
	749	M	130	50	40	-	rel. rapid injec.
	750	F	108	"	37	-	" " "
	751	M	110	"	37	*	" " "
	752	F	112	"	37	*	" " "
	733	M	135	60	42	*	" " "
	734	M	137	"	27	*	" " "
	735	F	122	"	27	*	" " "
	736	M	124	"	37	*	" " "
	793	F	125	"	65	-	rel. slow injec.
	794	F	124	"	65	-	" " "
	795	M	128	"	75	-	" " "
	796	M	127	"	62	*	" " "

Note: The amount of alkali used in preparation of solution 1.5 c.c. N/1 NaOH to each 200 mg. of drug.

Conclusions: With the more rapid rate of injection 75 per cent of the animals died within four hours, while with the less rapid rate only 16.6 per cent died.

desired and (2) that the introduction into the circulation of a relatively large volume of fluid is well tolerated. We have injected as much as 10 c.c. of physiological salt solution intravenously into a 100 gm. rat, within two to three minutes, without causing any observable symptoms.

A number of experiments (protocols not given) in which a 1 per cent solution was injected at the rate of 1 c.c. per minute, showed no definite difference in results as compared with those obtained with a 2 per cent solution injected only half as fast. No experi-

ments were made to show the effect on toxicity of increasing the concentration of the solution, the rate of injection remaining constant, but the reverse of these conditions caused a decided increase in toxicity. Two series of rats (see Table XI) were injected, the dose in mg. per kg. and the concentration of the solution being the same throughout. With the usual rate of injection of about 0.5 c.c. per minute, 2 of 12 died, while with this rate approximately doubled, 9 of 12 died. Eight additional animals were injected at the more rapid rate, with a dose 20 per cent lower. Four of them died within a short time, which indicates a very definite quantitative difference in favor of the slower rate of injection.

These experimental results are in keeping with those obtained from clinical experience. A study of the extensive data available at this laboratory, on the clinical use of arspenamine, showed that reactions seldom occurred when the dilute solution was used, even when the rate of injection was fairly rapid, and that conversely even a fairly concentrated solution seldom caused trouble, when the rate of administration was slow. The reports showed, however, that it was in clinics where the concentrated solutions were used, that most reactions occurred. It would not seem far wrong to state that dilute solutions, injected by the gravity method through a small needle, are potentially safe because several minutes at least will be necessary for the administration of the dose; while concentrated solutions are potentially dangerous because a full dose may be given within less than one minute. Giving the drug by syringe is particularly objectionable, because the solution used is necessarily concentrated and it is difficult to make the injection slowly enough. Few physicians control the rate by watch, and one minute often seems like five, when pushing the plunger of a large syringe, especially toward the end of a series of injections. Furthermore, painful infiltrations into the subcutaneous tissues occur more frequently in a clinic where the syringe method is used than in one where the gravity method is used.

#### SUMMARY OF RESULTS AND DISCUSSION

The work presented in this paper shows that the apparent toxicity of arspenamine is definitely increased, as established by fairly extensive animal experiments, by the following factors, and probably for the reasons specified:

1. By the use of animals of low resistance, because of inherent over-susceptibility, or because of actual physical inferiority.

2. Improper method of holding the animals, during the administration of the drug, producing thereby an abnormal state of excitation and physical exertion.

3. Pregnancy, on account of the animal receiving a relatively larger dose, in proportion to its own weight exclusive of the pregnant uterus.

4. Heating the product, in the preparation of solutions, by causing toxic by-products from rapid oxidation. A method is suggested to avoid the use of heat entirely, for products insoluble in cold water.

5. Alkali used in insufficient amount, by facilitating a precipitation of the product in the blood stream.

6. Rapid rate of injection, by favoring conditions which result in hemorrhages or thromboses.

In addition to these points on which definite evidence is presented; we believe, on the basis of our experience, that the apparent toxicity of arsphenamine is also increased:

1. In case of animals with loaded digestive tract.

2. By a too concentrated solution.

The reverse of all these conditions have the tendency to lower the apparent toxicity of the drug.

We believe that the results obtained in this work are comparable, in a general way, with those observed in man, and that care should be taken, in the clinical administration of arsphenamine, to avoid these various factors which increase the toxic effects of the drug. We have shown that wide variations, in the results with experimental animals, may be obtained, with the same lot number of arsphenamine, by varying the conditions of the experiment. It seems quite probable for similar reasons, that wide variations in the number of clinical reactions obtained with the same lot number of the drug, are largely attributable to variations in the technic of its preparation and administration.

An unusual number of reactions resulting from the clinical use of any particular lot of arsphenamine must be due to one or more of the following reasons: (1) "undue toxicity" of the product, (2) unusual susceptibility of the patients, and (3) failure to observe proper precautions in the administration of the drug. "*Undue Toxicity*" is the reason most commonly given as the explanation for the reac-



tions, whereas, most of the numerous reactions reported to this laboratory have, on investigation, been found to be due to errors in the technic of administration. The recommendations, for the administration of arspenamine and neoarsphenamine, made by the Surgeon General, U. S. Public Health Service, 1919, if followed, will beyond question prevent most of the serious reactions.

#### CONCLUSIONS

1. The toxic effects produced experimentally by the intravenous injection of arspenamine, are greatly influenced (1) by the health of the animal, (2) by the method of preparing the solution, and (3) by the technic of its administration.

2. If these conditions can be made uniform and constant, it is possible to detect relatively small differences in the toxicity of products.

3. Failure to obtain uniformity of these conditions may easily lead to erroneous conclusions as to the toxicity of a given product.

4. The results presented in this paper seem applicable for the explanation of some of the reactions resulting from the clinical use of arspenamine.

5. The physiologic standardization of arspenamine is not a simple matter. Judging from past experience, further changes in the Official Method for the testing of arspenamine, will be necessary, as our knowledge of the toxicology of the drug increases.

### Appendix

#### REGULATIONS

#### FOR THE CONTROL OF THE MANUFACTURE AND SALE OF ARSPHENAMINE

(1) Arspenamine shall not be sold in interstate traffic, or in the District of Columbia, or exported or imported except as provided herein.

(2) Arspenamine shall be offered for sale only in colorless glass ampules containing an atmosphere of inert gas, or in a vacuum.

(3) Each ampule shall be plainly marked so as to show the license number, the lot number, the name of the preparation, the actual amount of arspenamine in the container, and the name and address of the manufacturer, in the following manner:

“License No. \_\_\_\_\_

Lot No. \_\_\_\_\_

This package contains \_\_\_\_\_ grams of Arspenamine (hydrochloride of 3-diamino-4-dihydroxy-1-arsenobenzene) and conforms with regulations and tests prescribed by the U. S. Public Health Service. Made by \_\_\_\_\_.”

No names of diseases or symptoms shall appear on any label or package.

The name "Arsphenamine" shall be given precedence on the labels of containers and packages over the particular brand or trade name, and the size of type and display used for the name "Arsphenamine" shall be at least as conspicuous as that used for the brand or trade name.

(4) Each lot of the finished product shall be tested by the manufacturer for arsenic content and toxicity.

(a) *The total arsenic content* of the air-dried drug shall not be below 29.5% or above 31.6% when determined according to Lehmann's method as described in Public Health Reports, Vol. 33, June 21, 1918, page 1012.

(b) *The maximum tolerated dose* shall not be less than 100 milligrams per kilo bodyweight for albino rats when tested as follows:

(c) *Animals* must be well nourished and free from disease, weighing from 100 to 150 grams. Pregnant animals shall not be used.

(d) *Feeding and care of animals:* The rats should be fed on a well-balanced ration of white bread, cracked corn, cow's milk, and, in addition, twice weekly, fresh beef and cabbage. An adequate supply of fresh, clean water should be provided at all times. The rats should have no access to food for from eighteen to twelve hours preceding the injection, though water should be supplied during this time. During the period of observation following the injection the rats should be fed on the same mixed diet as described above.

(e) *Preparation of solution:* The shortest possible time should elapse from the opening of the ampule until the injections are completed. The drug is dissolved in freshly glass-distilled water and made into the alkaline solution by the addition of 0.9 c.c. N/1 sodium hydrate for each 0.1 gm. of the drug. The final concentration of the drug shall be in the proportion of two (2) parts per one hundred (100).

(f) *Method of injection.* This should be made into the saphenous vein by means of a burette or syringe, accurately graduated to 0.01 c.c.

(g) *Rate of injection:* This shall be at from 12 to 15 seconds for each 0.1 c.c. of the solution, and with the greatest uniformity obtainable.

(h) *No anesthetic* shall be used.

(i) *For each toxicity test* a series of not less than five rats shall be used, and at least 60 per cent of the animals injected must survive at least 48 hours from the time of the injection, provided that if the first test is made on five rats only and more than one die the test must be repeated and the final results based on the number of rats injected.

(5) In addition to tests made by the manufacturer before the drug is put in ampules, final tests of the product as prepared for the market shall be made on each lot by the U. S. Public Health Service before its release. For this purpose samples of each lot shall be forwarded by the manufacturer to the Hygienic Laboratory of the U. S. Public Health Service. The number of samples supplied shall not be less than ten (10) ampules from any lot, and from lots of over 1000 ampules one (1) per cent shall be furnished. Each ampule forwarded shall contain at least 0.6 gm. arsphenamine. Accompanying each lot, the manufacturer shall send a copy of the report of the toxicity test on which it was passed.

(6) Officers of the U. S. Public Health Service, when duly detailed, may enter establishments for the purpose of securing samples and conducting inspections.

(7) When lots have satisfactorily passed the prescribed tests they may be offered for sale, but the right is reserved to require the withdrawal from the market of any lot designated by the Surgeon General of the U. S. Public Health Service.

(8) Manufacturers shall retain two (2) per cent of the product from each lot for a period of three months from the time the preparation is placed on the market, provided that in no case this is less than ten (10) ampules of at least 0.6 gm. each.

### REGULATIONS FOR THE CONTROL OF THE MANUFACTURE AND SALE OF NEOARSPHENAMINE

These regulations are identical with those for arsphenamine with the following exceptions:

Throughout substitute neoarsphenamine for arsphenamine.

Par. 3.—This package contains ———— grams of Neoarsphenamine (a compound prepared from arsphenamine by means of formaldehyde sulphoxylate) and conforms with the regulations and tests prescribed by the United States Public Health Service. Made by———.

Par. 4. (1) The total arsenic content of the air-dried drug shall not be below 18 nor above 20 per cent when determined according to Lehmann's method as described in Public Health Reports, Vol. 33, June 21, 1918, Page 1012.

(2) The maximum tolerated dose shall not be less than 200 milligrams per kilo body weight for albino rats, when tested as follows:

(c) *Preparation of solution*: The solution should be made in a glass-stoppered cylinder in the shortest possible time with freshly glass-distilled water and the injections made immediately, as this solution changes rapidly in toxicity. Only cold water should be used. A preparation which is not readily soluble in cold, distilled water, should be discarded at once as a dangerous product. The final concentration of the solution shall be in the proportion of four parts per one hundred (100).

(d) *Method of injection*. This should be made into the saphenous vein by means of a burette or syringe, accurately graduated to 0.01 c.c. After the injection is complete the vein is ligated in order to prevent loss of blood. If a silk ligature is used, this should be removed on the following day.

(g) For each toxicity test a series of not less than five rats shall be used and at least 60 per cent of the animals injected must survive at least seven days from the time of the injection, provided that if the first test is made on five rats only, and more than one die, the test must be repeated and the final result based on the total number of rats injected.

Par. (5)—“0.6 gm. arsphenamine” should read “0.9 gm. neoarsphenamine.”

Par. (8)—“0.6 gm.” should read “0.9 gm.”



## ACKNOWLEDGMENT

I am greatly indebted to Prof. Carl Voegtlin, Chief Division of Pharmacology, and to Dr. G. W. McCoy, Director Hygienic Laboratory, for advice and assistance in connection with this work.

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# A STATISTICAL REPORT ON THE INCIDENCE OF CONGENITAL SYPHILIS

BY LAWRENCE T. ROYSTER, M.D., NORFOLK, VA.

(Received for publication, October 20, 1920.)

IN January, 1919, the King's Daughters' Children's Clinic began taking a routine Wassermann of all children who were brought to the clinic for treatment of any kind. The Wassermans were made by three different laboratories, but a large majority were made in one laboratory, by one person.\*

The object of this paper is to make a statistical report of the first thousand Wassermans taken.

TABLE I

Colored	659
White	341
Total	1000

TABLE II

PERCENTAGES	
Positive	125
Percentage of positives	12.5
Colored positives	101, or 15.47%
White positive	24, or 7.04%

TABLE III

AGES	
Youngest	1 mo.
Oldest	15 yr.
Under 12 mos.	35
1 to five yrs.	15
5 yrs. and up	75

\*The Wassermans were made by Dr. Mary E. Roche, Mrs. Maude Mansoni and Mr. H. G. Parker, the last of the Board of Health laboratory, who made most of the tests. I am indebted to Miss Mabel Wing for the keeping of the records of this series.

TABLE IV

PRESENTING CAUSE			
Swollen knee	1	Swollen cheek	1
Injuries	3	Nausea	1
Circumcision	1	Sore mouth	1
Skin eruptions	5	Glands of neck	1
Poor school work	2	Syphilis	1
Delinquency	2	Inflamed eyes	1
Pain in chest and back	1	Painful micturition	1
Enuresis	1	Discharging ear	1
Indigestion	1	Defective vision	7
General examination	7	Sore throat	6
Headache	5	Abscessed ankle	1
Earache	1	Whooping cough	1
Adenoids and tonsils	37	Feeding	42

This makes a total of 132, whereas, there were actually only 125 positive cases. The discrepancy of 7 is accounted for by the fact that where a child presented two conditions which did not appear to have any definite relation to each other, or to a common cause, they were tabulated separately.

TABLE V

CONDITION ON ADMISSION			
Of the 35 under 12 mos. the condition on admission as described by the examining physician was as follows:			
Good	7	Poor	18
Fair	6	Wretched	4
Of the 90 over 1 yr. the condition was described as:			
Good	27	Poor	26
Fair	34	Wretched	3

## DISCUSSION

*The clinic* is situated in Norfolk, a typical mid-southern city, with a population of 115,777 (not including suburbs) of which 75,256, or 65 per cent are white and 40,521 or 35 per cent are negroes. The city has a rather large foreign population. The clinic draws from the city proper and a large circumjacent territory, and has affiliations with various other philanthropic bodies, which refer cases needing special attention. Among these may be mentioned: the Juvenile Court, for whom we make mental examinations; the Society for the Prevention of Cruelty to Children and Children's Aid; the Colored Day Nursery, for whom we direct the feeding of infants whose mothers are compelled to work, while many school children are referred by the medical inspectors and school nurses.



The attendance during 1919, including new cases and returns, was approximately 5,000, while for the first eight months of 1920 there has been an average attendance of 600 per month.

#### RACE INCIDENCE

Among physicians of the South there is a popular classification of Negroes as regards syphilis, to wit: "Those who have or those who will have." This study has shown at least that the incidence of syphilis among negroes is about twice as great as among the whites, certainly so far as congenital infection is concerned.

#### CAUSE OF PRESENTATION

Merely as a matter of interesting detail a record was kept of the reason assigned by the parent or guardian for bringing each child to the clinic. A large number of these will be seen at a glance to bear no relation whatever to syphilis, while others are just as apparently of syphilitic origin. All of the cases of "skin eruption" were non-syphilitic. The cases of poor school work and delinquency (referred by the Juvenile Court) were apparently definitely related to the luetic infection. Some of the cases of headache were refractive in origin, while others were relieved only by specific treatment. All of the cases of "defective vision" were keratitis or choroiditis. Most of the "feeding cases" had syphilis as the underlying cause of malnutrition, a number being on an ample supply of breast milk. A few were apparently perfectly healthy. Most of the adenoid and tonsil cases presented no evidence of lues.

#### PHYSICAL CONDITION

As shown in Table V the luetic infection is reflected in the physical condition on admission, many cases classed as "fair" or "poor" showing no other evidence of syphilis than a malnourished or underdeveloped state. Of the 27 classed as "good," in the second division of Table V a majority were in cases of enlarged tonsils referred to the clinic by the school nurses as needing tonsillectomy. Of the 7 classed as "wretched" 6 were marantic infants, and one, a girl of 5 years who had both syphilis and tuberculosis.

#### CLINICAL

Unfortunately, on account of an insufficient number of physicians and nurses to keep the records complete during a part of the time

covered in this report, there were a number of errors made in recording certain complications and specific manifestations. It is therefore, impossible to tabulate the incidence of special symptoms. A generalization must suffice. As a rule, in early infancy marked malnutrition or marasmus was most frequently observed. This was particularly the case in breast fed babies; in fact, in almost every case in which a baby on an ample supply of breast milk was markedly undernourished, syphilis was the cause. Frequently this was the only manifestation. The buttocks of some of the marantic infants were excoriated from irritating diarrheal stools. The spleen and liver were frequently enlarged, but not with a degree of constancy which might be expected in syphilitic infants. The cases of epiphysitis were invariably in well developed and well nourished infants.

The special manifestations in older children were usually keratitis or choroiditis. Not one case in this series presented evidence of neurosyphilis. This is in striking contrast to the author's experience in private practice. There were four cases of typical Hutchinson's teeth; three were negroes and one white. Two presented the triad of deafness, keratitis and Hutchinson's teeth, while a third presented this triad with the addition of a "saddle" nose. There was not a single instance of "sabre" leg. Two cases of older boys exhibited such extreme ulceration as to lead to the suspicion of acquired lues.

#### TREATMENT

Little can be said of the results of specific therapy at this time, since many of the cases are still under treatment. This will be made the subject of a subsequent report.

# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

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WM. H. DEADERICK, M.D., EDITOR

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**Extra-genital Syphilomata.**—M. Truffi. *Giornale Italiano Delle Malattie Veneree e della Pelle*, 1920, vol. lxi, No. 2, p. 162.

In the course of the last four years, the author had occasion to observe a considerable number of cases of primary extragenital syphiloma, and although unable to give exact statistical figures, he believes that such abnormal primary localizations of the luetic virus are more demonstrable in larger proportions than heretofore, whether this be due to accidental factors or to the easier transportation of the infection by extragenital channels during the irregularities of warfare. His observations include some cases of very unusual localization, such as a primary syphiloma of the bulbar conjunctiva and another of the palpebral conjunctiva; a case of primary syphiloma of the back of the hand; four cases of syphiloma of the nipple, not due to suckling; seven syphilomata of the cheek, not due to the razor; finally, one case of syphiloma of the ala of the nose. It is noteworthy that the associated glandular involvement in the syphilomata of the cheek concerned not only the submaxillary but also the lateral cervical glands. In a woman 25 years of age, large papular lesions were demonstrable in the vicinity of the primary focus, resembling those noted on the genital organs in the environment of a primary syphiloma. The origin of the contagion in the case of primary syphiloma of the back of the right hand, in a man fifty years of age, remained entirely obscure. Here the syphiloma was of considerable size, luetic lesions of the trunk and limbs frequently attaining larger proportions than the genital sores. The epitrochlear glands showed no sign of involvement, but there was marked enlargement of the axillary glands. The seven primary syphilomata of the cheek were nearly all situated (with the single exception of one in the masseteric region) high up on the protuberance or just below the zygomatic arch.

**Unity of the Syphilitic Virus.**—Sicard, Paris. *La Presse Médicale*, July 28, 1920, vol. xxviii, 52.

The author offers numerous criticisms of the doctrine and experiments of Levaditi and Marie. Among these is the analogy of leprosy with its nervous and cutaneous forms. These are sharply marked off clinically but no



one seems even to have thought of neurotropic and dermatotropic *Handen's* bacilli. The same may be said of tuberculosis, the same strain of bacillus being capable of causing the most opposite clinical types. From analogy there should be a pneumotrope tubercle bacillus and an osteotrope or meningotrope form. On the field of experiment Sicard meets Levaditi with inoculations of two paretics with treponemes from a cutaneous lesion. The result was negative and was in agreement in this respect with results of old experiments by Krafft-Ebing. In the clinic many analogous finds are seen which do not point toward dualism. The author concedes that metasyphilis is seldom preceded by dermosyphilis save in an apparently attenuated form, but tropism is not absolutely necessary to explain this fact. The subject may have considerable natural immunity to the disease, as shown by the mild and brief secondary period, but this immunity is not so complete as to prevent the remote appearance of lesions nor perhaps is the immunity permanent for life. Evidence has been adduced which tends to show that metasyphilis may resemble an allergic phenomenon. Thus in mild secondary syphilis the skin and mucosa may lead to an adaptation-reaction which need not apply to the nervous centers; and as a result there will be no further dermcutaneous syphilis. In severe dermcutaneous syphilis this adaptation has not occurred but the spirochetes exist only in these regions of the body. The strongest argument for unicism is in the failure of treatment of metasyphilis by spirilloicide remedies.

**The Effect of Weak Acetic Acid on *Spirocheta Pallida*.**—Journal of the American Medical Association, 1920, vol. lxxiv, 803.

Goodman in a preliminary communication notes the effect of weak acetic acid on *S. pallida*. On the basis of the clinical observation that syphilitic chancres are very infrequent in the vagina, which is normally acid in reaction, and the microscopic examination of spirochetes under the dark-field prior to and after the addition of acetic acid, Goodman is led to believe that acids have a lethal effect on the causative organization of syphilis. He proposes that a wider study be made as it appears that an acid solution such as weak acetic acid may be of use in the prophylaxis of syphilis.

**Experimental Syphilis in the Rabbit. II. Primary Infection in the Scrotum.**

**Part 2. Scrotal Lesions and the Character of the Scrotal Infection.**—Wade H. Brown and Louise Pearce, New York. Journal of Experimental Medicine, 1920, vol. xxxi, p. 729.

From a study of the reaction to scrotal inoculation *Treponema pallidum* in a large series of rabbits, it was found that the specific reaction presented the following characteristics. In general, the reaction in the scrotum became apparent within 7 to 14 days after inoculation but was subject to considerable variation. The early reaction took the form of an edematous swelling and congestion associated with a new growth of vessels or of an infiltration with more or less proliferation of fixed tissue cells. These reactions were either confined to a small circumscribed area of the scrotum or were of a diffusely spreading character, and as the infection advanced, the infiltration and proliferation, together with such

secondary changes as exfoliation, necrosis and ulceration, became the most conspicuous features of the reaction. The course of the reaction in the scrotum was essentially the same as that in the testicle; that is, it was periodic in character and was marked by a phase of active progression followed by quiescence or regression and renewed activity. The scrotal reaction resembled that in the testicle also in the varying character of the reaction, appearing at times as a circumscribed focus of reaction and later becoming diffuse, or first as a diffuse reaction which subsequently became more localized. The lesions produced in consequence of this reaction were of two general types—one a circumscribed indurated granulomatous lesion closely resembling the human chancre, the other a diffuse infiltration more analogous to the secondary skin lesions of man. Both groups of lesions presented the greatest degree of individual variations and possessed no fixed status but were subject to frequent and marked transformations. After a period of from a few weeks to many months, the lesions in the scrotum disappeared spontaneously.

**Experimental Syphilis in the Rabbit. III Local Dissemination, Local Recurrence, and Involvement of Regional Lymphatics.**—Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1920, vol. xxxi, p. 749.

From a study of the phenomena of the primary infection on the one hand, and the phenomena of local spread, or dissemination, on the other, it is seen that a multiplicity of lesions develops in the testicle and scrotum of the rabbit which have much the same characteristics irrespective of their origin. Some of these lesions are clearly recognizable as primary lesions or parts of a primary reaction to infection, while others are just as clearly the results of dissemination of the virus from a primary focus of infection or correspond with lesions which are commonly spoken of as secondary lesions. The effort to draw a sharp line of distinction between these two groups of lesions or between a primary and a secondary stage of infection in the rabbit, however, would be largely an arbitrary procedure. The fact is that the tissues of the scrotum and testicle of the rabbit constitute favorable surroundings for the localization and development of pallidum infections. Under ordinary circumstances, a large part of the reaction to infection which expresses itself in the formation of lesions recognizable by ordinary methods of examination takes place in these tissues. These lesions present certain broad and general characteristics without regard to whether they are primary or secondary in origin; the reaction is merely a reaction to a syphilitic infection which in either case may assume the most diverse character. Further, it would appear that in rabbits infected with such strains of *Treponema pallidum* as we have used, the virus is never confined to the area occupied by the so-called primary lesion, or chancre, but always spreads and always gives rise to a regional adenopathy. There may be no lesions to indicate the progress of this dissemination, but an examination of the inguinal nodes shows that dissemination occurs very soon after inoculation, and a pallidum reaction may be detected in these glands even before infection can be recognized in the scrotum. Subsequently, lesions develop in all parts of the scrotum and testicle, sometimes involving the entire testicle or scrotum, and at others, forming focalized lesions with an especial predilection for



certain locations such as the epididymis, the mediastinum testis, the tunics, and the dorsal folds of the scrotum. In some instances, more or less continuous lesions form along the course of the perivascular lymphatics, suggesting that this is one path taken in the dissemination of the organisms. It is probable, however, that lesions of a gross character develop more as a result of accumulation of spirochetes than of mere invasion of the lymphatics since they are not a constant accompaniment of the local infection, while invasion of the lymphatics and extension of the infection to the regional lymph nodes occur in all cases.

**A Case of Luetic Reinfection Fifteen Years after Primary Syphilis.**—Brandt, R. Wiener medizinische Wochenschrift, 1920, No. 6, p. 278.

The author's observation concerned a woman (prostitute) thirty-three years of age who was under treatment in Neumann's clinic fifteen years ago, for an abundant papulous eruption, receiving eighteen inunctions. She was discharged cured and underwent no further antiluetic treatment, until recently she was attacked by frequent headaches, for which eight mercury injections were administered. Some months later she was admitted to the Frances-Joseph Hospital for Women Suffering from Venereal Diseases, and a typical sclerotic lesion was noted on the inner surface of the left labium minor. Spirochete pallida were demonstrable, although in small numbers, on dark-field examination. Wassermann reaction was at first negative, but became positive a week later, at the time of the appearance of a papular eruption on the trunk. The occurrence of a reinfection is positively indicated by the clinical appearance of the lesion, the further course, the demonstration of the spirochete, and the behavior of the Wassermann reaction. Treatment consisted of hydrarg. salicylic injections and neosalvarsan, altogether 6 Hg and 5 neosalvarsan at 0.60. The erosion had entirely healed three days later, and the Wassermann serum reaction became negative soon afterwards. The spinal puncture fluid two and a half weeks later showed faint traces of a Wassermann reaction. The patient was discharged cured about two months after admission. The case is noteworthy precisely on account of the long interval between the first and the second infection, this being apparently typical of luetic reinfection after treatment with mercury alone. Conditions are altogether different in reinfections following salvarsan treatment, and Benario's compilation shows that one-half of the cases occurred within six months after the end of the medication. In this mode of treatment, the tissues return much more rapidly to their original condition, proving the higher efficiency of salvarsan as compared with mercury.

**Infectious Character of Latent Syphilis.**—E. Friedlaender. Deutsche medizinische Wochenschrift, 1920, No. 21, p. 572.

The author discusses the dangers of latent spirochetosis and its treatment by the intravenous route. The efficiency of intravenous treatment of general paralysis and late syphilis has been proved by practical experience, in the author's work and that of others, besides resting on solid theoretical foundations, for it has been shown that the spirochetes in a large number of cases are



carried in installments by the hematogenous route. Their seat of predilection is especially in the paralytic brain, in the walls of the large blood vessels and their immediate surroundings, where they can often be demonstrated in enormous masses. Upon these reliable findings is based the new intraarterial procedure, in which salvarsan is injected directly into the common carotid artery. The results which have been accomplished by Knauer, the originator of this method, again serve to show that the control of the late syphilitic affections of the central nervous system by the hematogenous route is actually the most promising mode of treatment.

All syphilitic patients, by no means only those having latent syphilis and later on developing paralysis, must be regarded as the carriers of dangerous bacilli. This viewpoint is not only theoretically well grounded on the latest findings, but it also possesses the greatest importance for practical hygiene. The fact must be emphasized that the spirochetes still existing in the body in latent syphilis represent a permanent danger for the carrier of the spirochetes himself as well as for his environment. Keeping in mind that all the affections which were formerly described as metaluetic and which according to current investigations simply represent spirochetoses of the central nervous system, are derived from an originally latent syphilis, the source of dangers from a latent spirochetosis must be estimated as even greater than the dangers of latent tuberculosis for the carrier as well as for his surroundings. It is highly probable that the number of extragenital transmissions through individuals having latent syphilis is much greater than was hitherto assumed, although the existence of such a connection can rarely be positively established. It must therefore be the physician's endeavor to institute abortive treatment not only in all recent cases of syphilitic infection, as far as possible, but also to discover all latent syphilitic patients and to subject them to energetic treatment, until the clinical and serologic findings justify the assumption that they no longer harbor the spirochete.

**Plurality of Syphilitic Germs.**—Pagniez. *La Presse Médicale*, 1920, No. 27, p. 266.

Certain clinical observations have led to the assumption of a variety of treponema having specific affinity for the nervous system, and differing from the spirochete which gives rise to ordinary syphilis. At the present state of laboratory technic, it is possible to compare from the viewpoint of their biological properties, the virus derived from general paralysis and the virus derived from the chancre, namely, the neurotrope and the dermatrope virus. The recent investigations of Levaditi and Marie (1919) of these two types of syphilitic virus have led to results indicating what may be described as a plurality of the pathogenic agent. The onset of parasymphilitic disturbances is presumably due in a certain number of cases, to contamination by a strain of spirochetes possessing a more or less marked affinity for the nervous system. This treponema would be capable of readily adjusting itself to the brain and cord centers, and gradually undergoing transformation into a variety with fixed properties, in the form of a practically exclusive affinity for the nervous

system. The treponema of general paralysis is not merely a germ with attenuated virulence, but must be considered as a different variety from the spirochete of cutaneous, mucous, and visceral syphilis. Between these two types of syphilitic virus exist differences analogous to those observed between strains of spirillum in other diseases. But the problem has not yet been entirely elucidated, and further experimental investigations are highly desirable along this line of inquiry. From the extension of our knowledge of the spirochete and its varieties may be expected some valuable indications concerning the treatment of parasyphilis.

**Experimental Vascular Syphilis.**—Bayet, Bruxelles. *La Presse Médicale*, May 29, 1920, vol. xxviii, 35.

Experimental syphilis is only in its infancy and but little has been done in the line of vascular syphilis, about the only study being that of Vanzetti in 1911. This state of affairs is readily intelligible because of the difficulty of preparing good inoculable material and because animals perfectly suited for certain experiments are difficult to obtain. Then again the observation period in vascular syphilis must be a long one and many accidents may happen. The type of experiment may be varied as follows: we may produce generalized infection from a given focus and investigate the vessels for specific lesions, or we may throw the culture or specific tissue directly into the blood stream or finally the spirochetes may be inoculated directly into the vessel wall. The latter route was chosen by Vanzetti who produced conditions which recalled those of specific arteritis and aneurysm. It is not necessary that syphilomata be produced and further the arterial lesions according to Vanzetti may be produced, even without the presence of the spirochete *in situ*. This phenomenon called by Bayet treponemolysis is very difficult to explain. It is always difficult to demonstrate the presence of the treponema in the vascular lesions, even when it is known to be present. One explanation which is akin to the preceding is the direct action of the toxin of the spirochete. The fact that syphilitic vascular disease occurs in patches is difficult of explanation by the theory of spirochete colonization *in situ* although the toxins might be conceived to exert a special tropism for certain areas. A third hypothesis has reference to sensibilization of the tissues to the toxin. It is evident that these hypotheses do not exclude one another and the author indicates merely a threefold type of activity.

**Hereditary Syphilis and New Syphilis: Hypersyphilis.**—Goubeau. *Bulletin de la Société Française de Dermatologie et de Syphiligraphie* 1920, No. 3.

A heredosyphilitic may contract the disease *de novo* and it may begin like any acquired syphilis with a chancre followed after brief delay by secondary symptoms. The crucial point is this—Is the inherited disease extinct or merely latent? Are the stigmata of the old disease no evidence of an acquired immunity to further infection? The author is satisfied that treponemata still persist in the tissues, but that through a process of adaptation they

have become inactive. Fresh spirochetes from without may now prove infectious and may even add to the gravity of the case—in other words we have superinfection, or as the author terms it hypersyphilis. The author appears to believe in the reverse of immunity, in a supersensitiveness of the organism due to the earlier sensitization by the inherited disease. This state of affairs can only be visualized by cases in point, for much evidence exists of the opposite character, showing that some heredosyphilitics are wholly, while others are partly, immunized. The first case cited was in a man with many stigmata of the inherited disease and a history of parental syphilis. His 16 year old son also presents stigmata. After having lost his wife the subject contracted malignant syphilis comprising a huge phagedenic chancre and ulceroserpiginous syphilides with severe constitutional reaction. Despite energetic treatment the throat showed ulceration 8 months after infection. Intensive treatment finally caused the recession of all symptoms. The period of latency in this case between active hereditary and acquired manifestations was 12 years. In discussion several well-known syphilographers insisted that as a rule hereditary syphilis conferred considerable immunity to acquired syphilis and “attenuated” the virus, so to speak. Thibierge, however, stated that in the experience of the Russians “binary syphilis” was often severe.

**Syphilis Insontium.**—J. C. McWalter, R. A. M. C. *British Medical Journal*, 1920, No. 3103, p. 827

Infection of a mother with syphilis in the eighth month of her pregnancy results in infection of the child. The syphilis in the child is of a milder form and develops later than ordinary congenital syphilis. Infection of the mother with syphilis in the later months of pregnancy may have no deleterious effect on her confinement. There are some cases of syphilis insontium capable of the most rigid proof.

**Morphological Variations of the Spirochete Pallida in the Brain of Paralytics.**  
—G. Sprenger. *Archives für Psychiatrie und Nervenkrankheiten*, 1920, lxi, p. 479.

On examining a considerable number of sections from different brains of paralytic individuals, the contained spirochetes will be found to present well-marked variations in caliber and length. This peculiarity was especially pronounced and extensively distributed in several portions of the brain cortex derived from a case recently observed in the Frankfort Psychiatric Clinic. The patient died in his twenty-fifth year, after having shown symptoms of dementia for about six months. The autopsy showed leptomeningitis, cerebral hyperemia, and atrophy of the frontal lobe. In view of the anamnesis and the early onset of the disease, the possible existence of juvenile paralysis could not be excluded. The microscopic examination of this brain confirmed the clinical diagnosis. The soft meninges were locally interspersed, with cellular elements, primarily plasma cells. The cortex was distinctly narrowed in several localities, and its structure was altered; the vessels were increased in



number, and diffuse, for the most part very considerable, cellular infiltrates were noted in the lymph sheaths and the vascular walls. In some localities, atrophic changes of the ganglion cells were seen in smaller or larger areas, and the cortex was abundantly interspersed with rod cells and decomposition products. The glia locally presented active proliferation. Specimens treated according to Jahnke's procedure showed that the very numerous spirochetes possessed, almost throughout, a very unusual length and delicacy. The length of the individual spirochetes in a general way amounted to at least twice, usually three times, the length as ordinarily seen in paralytic brains. The number of convolutions, which otherwise varies between eight and thirteen, occasionally in a small percentage of cases reaching twenty to twenty-four, here amounted for the most part to twenty-six to thirty, even up to thirty-two convolutions. The convolutions were mostly flattened in their entire extent. The thickness was considerably diminished throughout. For long distances in the left upper frontal convolution, it was difficult to recognize the fairly abundant diffusely scattered hair-shaped parasites, on account of the extreme delicacy of the thread-like structure. The scattered spirochetes were frequently curved in the middle or elsewhere and irregularly twisted. Where the parasites were collected in larger masses, this feature was not so pronounced. Close to the elongated and bent structures, well developed and nearly straight spirochetes could often be seen lying in the tissues; showing that the changes in configuration were not due to artifacts or postmortem phenomena. Although flattened convolutions were the rule, other forms were also encountered in the midst of the threads, which, aside from their abnormal length, closely resembled the normal picture of the *Spirochete pallida*, presenting fine, close convolutions and almost normal thickness. Such forms were seen in larger numbers in the groups, colonies and collections found in this case as in many others, besides a diffuse distribution of the spirochetes in the parenchyma.

Regarding the general and special distribution of the spirochete, the brain substance was invariably free, whereas all the cortical layers harbored spirochetes, the thread-like configuration being, as a rule, more marked in the upper than in the deeper layers. Larger collections and foci were found especially in the upper layers, but also in the fifth and sixth layer. Long distances showed only a diffuse, sometimes very scanty distribution of the parasites. Frequently the spirochetes could be seen lying in small bunches of long threads; sometimes they surrounded the glia cells, more rarely a ganglion cell. The larger accumulations of spirochetes were observed comparatively often in the vicinity of small capillary vessels. The various collections seem to exist independently or to communicate with each other, the latter mode being apparently the most common.

**The Pathology of Congenital Syphilis.**—J. Frank Fraser, New York. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 491.

The case here reported is one more to be added to those of apparently non-syphilitic and immune mothers bearing children that have been proved syphilitic. From a review of antenatal pathology and embryology and the morpho-

logic evidence in this case, as indeed in all cases of congenital syphilis, it would appear that infection takes place only after the fetal organs have been formed—a fact which excludes the theory of germinal transmission unless we assume a practically unsupported theory of “larval inactivity” of the infecting organism. From the facts reviewed the most plausible explanation of the 5 per cent residue of nonsyphilitic and immune mothers of syphilitic children is that these mothers have a mild, low grade form of syphilis.

**Two Cases of Tonsillar Chancre.**—R. Renou. *Revue de Laryngologie d'otologie et de Rhinologie*, 1920, vol. xli, p. 538.

The two cases observed by the author are reported on account of their unusual symptoms and the diagnostic conclusions resulting therefrom. The first patient, a man forty years of age, was sent to him with the diagnosis of malignant tumor of the tonsil (carcinoma); the true condition was atypical chancre of six weeks' standing, of the erosive type. The surface of the purplish-gray and superficially eroded tonsil was covered with thin exudate consisting of endothelial cells and polynuclears. The difficulty of the diagnosis was due to the small size of the tonsil, the inconsiderable glandular enlargement, and the apparent localization of the lesions at the level of the faucial pillars rather than the tonsil, which looked as though set in a hard, red, sausage-shaped frame, formed by the pillars of the velum. Secondary symptoms being absent, all doubts were removed by the prompt efficiency of antiluetic treatment in the form of combined mercurial and arsenical medication. The Wassermann test was very positive. The second patient, a man twenty-six years of age, was admitted to the Lyon Hospital suffering from right-sided submaxillary swelling and slight dysphagia. There was neither ulceration nor erosion of the tonsil, not even induration (at least at the time of examination), but merely a simple hypertrophy of the organ, in no way different from that seen in the course of an ordinary tonsillitis. The diagnosis could be based on the features of the voluminous, hard, painless, unilateral swelling of the submaxillary glands, without periadenitis, as well as upon the coexistence of a confluent roseola. Such pronounced characteristics of the glandular involvement are almost pathognomonic. The early appearance of the roseola in this case (two or three weeks after the onset of the chancre, instead of six or seven weeks later, as usual) is not surprising, in view of the observation that the invasion of the organism occurs much more rapidly when the syphilitic virus is inoculated through the tonsil than through any other region of the body; as a result, secondary symptoms are often already present when the tonsillar chancre is discovered. This second case belongs to the so-called anginous form of Fournier or the simple hypertrophic form. It was atypical; first, by the absence of tonsillar induration; second, by the absence of all visible erosions. In some cases, this erosion must be looked for at the level of the upper pole of the tonsil or behind the anterior pillar. In other cases, as in the present instance, it is probably invisible because instead of occupying the surface of the organ it is situated on the floor of the tonsillar crypts.



Having nothing in common as regards the appearance of the lesions, these two cases resembled each other only by their subjective signs, local and general. Locally, dysphagia was noted in both cases, rather severe in the first patient, where it was of six weeks' standing and accompanied by otalgia, less marked in the second case, when it dated back only a fortnight. It is noteworthy that prolonged dysphagia is a symptom of great diagnostic importance in these cases. A febrile period of some days was noted in both patients, characterized by general disturbances (malaise, anorexia, chills, prostration, fatigue, lassitude) and by the aggravation of the dysphagia. This period probably corresponds to the invasion of the organism by the spirochete and to a tonsillar exacerbation due to a temporarily increased virulence of the microbes normally present in the region of the tonsil. The existence of these general symptoms in the course of tonsillar chancre is very important to remember, being the source of numerous errors and confusions of incipient luetic disease with simple angina. All syphilitic chancres tend to undergo a spontaneous cure in some weeks, averaging from five to eight, which is not desirable in so far as it mitigates against the early recognition of syphilis and the timely institution of treatment. Sometimes after the disappearance of the chancre, the satellite bubo persists long enough to permit a retrospective diagnosis. Many cases of tonsillar chancre probably remain undiscovered because its occurrence is not kept in mind and its variegated clinical features are not sufficiently known. Much less importance should be attached to the variable appearance of the tonsillar lesions than to their unilateral character, their induration, and the classical associated glandular involvement, which always outlasts the chancre.

**Syphilitic Leucoderma and Alopecia.**—H. Koenigstein. *Wiener medizinische Wochenschrift*, 1920, Nos. 30-32, p. 1351.

Syphilitic alopecia and leucoderma are related phenomena, and the two conditions are not only frequently combined, but transitions are seen between depigmented spots on the neck and bald spots on the occiput. The similarity is also illustrated by occasional discoloration of alopecic foci on the one hand, and loss of hair on leucodermic spots on the other. The histologic findings in alopecic foci are likewise suggestive of the findings in leucoderma. Alopecia is a less common symptom than leucoderma, which was represented in the author's material of 2010 syphilitics by 517 cases, or 25.6 per cent, as compared to 272 alopecias. This means that among one hundred patients with secondary syphilis, including latent lues, there are sixteen cases of alopecia. Judging from the author's material, the development of specific alopecia seems to be even more dependent than the evolution of leucoderma on the early stage of lues. Among ninety alopecias originating under his observation, only six cases developed after one year and five later than two years after the infection. The absence of alopecia in later years of lues is also accounted for by the essentially more rapid healing of alopecic foci than leucodermic spots. As the ingrowing hairs usually possess at once the same pigment contents as before, the reestablishment of the former condition is accomplished more rapidly than in leucoderma, being usually attained at the end of three to six months.



The positive findings in the puncture-fluid of patients suffering from secondary syphilis at first rapidly increase in frequency with the progress of the disease, reaching the highest number in the tenth month, after which they gradually diminish again. The anticipation of positive or negative spinal findings in the presence of a luetic symptom of the first year, is essentially governed by the number of months which have elapsed since the infection. Only syphilis with alopecia, and in part also those with leucoderma, are not subject to this law. Positive findings in patients with alopecia were noted by the author before the fourth month in 79.5 per cent, up to the sixth month in 83.3 per cent, up to the eighth month in 78 per cent, up to the twelfth month in 88.2 per cent, and in cases of more than a year's standing in 75 per cent. The figures accordingly remain at the same level in nearly all periods. These findings are usefully supplemented by the statement that according to the author's results, syphilitic patients in the fourth month of the infection show changes of the spinal fluid only in 28 per cent of the cases. The following figures indicate the positive puncture findings in patients with leucoderma in the various periods: Up to the fourth month, 46.6 per cent; up to the sixth month, 40 per cent, up to the eighth month, 64.5 per cent, up to the twelfth month, 69.5 per cent, up to the end of the first year, 70.8 per cent; in cases of two or more years' standing 34.6 per cent. As luetic individuals average no more than 28 per cent positive puncture findings up to the fourth month, it follows that cases of leucoderma start in a far greater number. Luetic patients with leucoderma also show a higher measure of positive puncture findings up to the end of the first year than patients without leucoderma and alopecia. The following figures furnish still more detailed information concerning the positive spinal findings in the presence of leucoderma. Of 326 cases associated with leucoderma and various other symptoms, including alopecia, 110 gave a positive reaction (66.2 per cent). After exclusion of all cases which were simultaneously affected with alopecia, there remained among 187 patients 104 with positive spinal findings (56 per cent). Omitting the cases of more than a year's standing, the number of positive reactions is increased to 58 per cent.

**Two Rare Localizations of Syphilis (Acute Luetic Myringitis and Thyroiditis).—**C. Castigliola. *Archivo Italiano di Otologia, Rinologia e Laringologia*, 1920, vol. xxxi, p. 59.

Isolated luetic manifestations on the part of the tympanic membrane, with slight involvement of the middle and internal ear, as in a case observed by the author, are extremely rare. The patient was a soldier 24 years of age, who was admitted to the hospital with bilateral progressive hardness of hearing, of about six weeks' standing, without other local or general disturbances. There was no history of preceding aural or rhinopharyngeal disease. Otoscopic examination showed reddening of the upper posterior portion of the external auditory meatus and of the entire tympanic membrane, on which round rose-colored spots were seen, with well-defined outlines, irregularly distributed over the several quadrants. The findings in the two ears were very similar, although the spots appeared rather more numerous and the tympanic membrane

more infiltrated on the right side. Functionally, air-conduction was almost completely abolished on the right side, to a less degree on the left, where ordinary speech was heard at only about 20 cm. distance. A loud ticking watch was heard on the right side only in the direct vicinity of the concha, whereas bone-conduction remained good. The examination of the static and dynamic equilibrium had a negative outcome. In spite of the obscure history of a recent venereal infection and the absence of specific phenomena in the clinical physical examination, the pathogenesis of this aural affection could be referred with a high degree of probability to secondary lues, in view of the essentially insidious progressive evolution of the disease without elevation of temperature or pain, and the otoscopic findings. At the onset, the syphilitic skin eruption had probably extended over the entire auditory meatus, in view of the presence of enlarged preauricular and mastoid lymph glands. The diagnosis of lues was confirmed by the positive outcome of the Wassermann reaction and the results of specific treatment. Endovenous salvarsan medication, combined with mercury, led after about ten days to the complete disappearance of the spots from the tympanic membrane and to the rapidly progressive return of the normal hearing capacity in both ears, so that the patient after a month's energetic mixed treatment could be discharged entirely cured of the ear trouble and fit for regular military service.

The second observation concerned a case of acute specific thyroiditis with sudden severe compression of the first portion of the trachea, in an Arab boy five years of age suffering from late congenital syphilis. The thyroid enlargement was symmetrical, of rather hard and inelastic consistence, without pulsation; the isthmus of the gland was abnormally enlarged. During the examination, the patient was in a semi-asphyxiated condition, with all evidences of extreme dyspnea, indicating the immediate performance of tracheotomy. Six hours after the intervention, the normal function of the respiratory and cardiovascular apparatus having become reestablished, the patient was given an endovenous injection of 30 gr. of neosalvarsan under all necessary technical precautions. By means of mixed specific treatment, continued during a month, the postoperative course was rendered very favorable, with rapid subsidence of the thyroid enlargement during the first eight days. The cannula could be definitely removed at the end of eleven days. The patient was repeatedly seen again since his discharge from the hospital, in good general and local condition; the lobes of the thyroid gland had resumed their normal size and consistence, and the surgical wound had firmly united. In a very similar unpublished case, Prosdocimo recently performed tracheotomy as an emergency procedure on a young Arab with secondary syphilis, threatened with asphyxiation through tracheal compression by acute hypertrophic thyroiditis of specific origin. Mixed treatment proved highly beneficial also in this instance.

**Evolution of Acute Nephritis in Hereditary Syphilitics.**—Queslier. *Gazette des hôpitaux*, July 20-22, 1920, vol. xciii, 64.

The author has found in literature 101 cases in which the specificity of nephritis was established by the avowal of the parents, stigmata of the



inherited disease and positive seroreaction. Of this number 73 were under two years of age while the remainder were of all ages up to twenty-three years. In all of these cases other prominent causes of nephritis could be excluded. In addition to the 101 cases she found 21 others in fetuses and stillborn children, making the total 122. But 6 of the 73 infants survived the disease while of the 29 older individuals 18 succumbed to the nephritis. The latter was of no one type for all varieties were represented—gummosis and amyloid, along with the ordinary forms of parenchymatous and interstitial nephritis. As this paper deals only with acute types the number represented in the autopsy finds comprises 13 cases of acute interstitial nephritis and 10 mixed ones in which an acute was grafted on an old case. The author is not clear as to acute parenchymatous nephritis in autopsy but in the clinic this appears to have been common. Since the cases almost always ended fatally the absence of acute parenchymatous nephritis at autopsy is not readily understood. Either the symptoms must have been misleading or the condition must have changed before death, but there is mention of but 7 cases of the parenchymatous form at autopsy without reference to stage; the only conclusion to draw then is that symptoms in the young child suggestive of acute parenchymatous nephritis are due in reality to acute or subacute interstitial nephritis with beginning sclerosis. She implies however that renal symptoms are often masked by extensive lesions of other organs. Extensive sclerosis was never found. The six recoveries are attributed to timely mercurial treatment.

**A Case of Syphilis of the Stomach.**—L. Ramond. *Le Progrès Médical*, 1920, No. 1, p. 7.

The case observed by the author concerned a woman forty-six years of age and was characterized by the following features: (1) Syphilitic infection at the age of twenty-one years. (2) History of cutaneous syphilides during five years. (3) Occurrence of hematemesis, in three attacks, at long intervals, since fourteen years. The blood was undoubtedly derived from an ulcer of the stomach, which had to be traced to its origin and under the circumstances was readily attributed to syphilis. This gastric ulcer had recurred for the third time in fourteen years; in the interval, the patient had presented obstinate and persistent ulcerations of the skin. She suffered from syphilis twenty-five years ago, and the luetic infection was held responsible for the cutaneous manifestations. The gastric symptoms could therefore be referred to the same origin especially in view of the fact that the medical literature contains numerous observations on ulcerative syphilis of the stomach, of hemorrhagic type, closely resembling the condition noted in the present instance. All these cases were characterized by profuse recurrent hematemesis, followed by severe anemia, coinciding or alternating with ulcerative cutaneous manifestations, in individuals infected with syphilis. The cutaneous lesions and the gastric symptoms disappeared in all these cases through antisyphilitic treatment, thereby furnishing proof of their real character. However, although ulcerative gastric syphilis of hemorrhagic type is one of the most common forms of syphilis of the stomach, other cases may present a misleading picture of can-



cer, or of simple chronic gastritis, with vomiting, pain, and anorexia, but no hemorrhage. In typical cases of pseudocancer of the stomach, with predominant signs of pyloric stenosis, gastric syphilis may closely simulate cancerous stenosis of the pylorus. Occasionally, it gives rise to a mediogastric stenosis, leading to the deformity known as bilocular stomach. Such cases, controlled by radiologic examination, have been known to recover under specific treatment.

The diagnosis of lues in all these cases was based solely upon the association of gastric disturbances with cutaneous or mucous lesions, and upon the beneficial influence of specific treatment. Numerous autopsies have been recorded, however, followed by histologic examinations, which have permitted a distinction between several anatomic types, from diffuse syphilitic gastritis to luetic ulcers originating through gummatous lesions. Syphilis of the stomach is not very common, but it is probable that many cases remain unrecognized. The disease has been observed at any age, between twenty-three and seventy-three years, usually supervening in adults as a tertiary lesion, from two to forty years after the chancre. The functional digestive disturbances of the secondary period do not represent a secondary syphilis of the stomach, only three authentic cases of which have been reported in the form of gastric ulcers supervening in the first months of the infection and promptly yielding to mercurial treatment.

The recognition of syphilis of the stomach is based in the first place on its possibility being kept in mind in every case of severe gastric trouble, especially when various forms of treatment have proved insufficient or useless. A luetic history should be looked for, and the diagnosis will be strongly supported by associated syphilitic lesions of the skin, the viscera, the nervous system, the scars of old syphilides, a positive Wassermann reaction, and so forth. A favorable influence of antisyphilitic treatment will confirm the assumption of gastric syphilis. Arsenic, mercury, or iodide may be employed, mercury being the most important, although a few remarkable cures have been obtained by potassium iodide alone, which is usually administered as an adjuvant of mercury or arsenic. All the entrance avenues of these remedies may be utilized, including administration by the mouth, although this is not the most desirable mode of administration.

**Examination of the Eighth Nerve in Recent Lues; Irritability before and at the End of a Combined Course of Mercury and Salvarsan.**—F. Kobrak. *Beiträge zur Anatomie, Physiologie, Pathologie und Therapie des Ohres, der Nase und des Halses*, 1920, vol. xiv, 101.

The static labyrinth frequently reacts to compression of the auditory meatus, in the absence of a labyrinth fistula, in syphilitic patients. This reaction, however, is characteristic not only of lues, but also of special irritative conditions of the vestibular nerve in general. There is an abnormal irritability observed in lues as well as in other diseases, rather than a paradoxical reaction belonging to lues exclusively. The percentage of involvement of the

eighth nerve, without clinical symptoms, is remarkably high, although usually of a low degree. Only nineteen cases in a material of one hundred were unobjectionally free from any symptoms on the part of the eighth nerve. Ophthalmologic serial examinations showed a much smaller percentage of involvement of the eye in recent syphilis, than the author was enabled to note in the ear. The functional method of ear-examination evidently reveals the nervous condition more clearly than the ophthalmologic method of inspection.

Isolated cochlear affections do not seem to be more common in recent lues than isolated vestibular affections. The former are more frequently observed in females than in males, judging from the author's material. The fact that distinct cochlear affections were much more common in women than in men would seem to indicate that the frequently existing war-lesions of the labyrinth among the examined men create no predisposition for luetic or other infections of the labyrinth. Cases with a still negative Wassermann reaction and an already positive labyrinthine condition, without subjective disturbances, are of fundamental importance and prove the correctness of Ehrlich's theory that the premature lesions of the cranial nerves after salvarsan are to be interpreted as neurorecurrences. The complications in salvarsan cures seem to depend upon the same conditions in the earliest and in the late stage of syphilis. The fact that primary lesions with a still negative Wassermann reaction may already be associated with metastases in predisposed localities, permits doubts as to the reliability of early abortive treatment. Further observations on early localization of lues in cranial nerves while the Wassermann reaction is still negative, would go to show that a negative outcome of the Wassermann reaction is not a reliable criterion of the absence of general specific infection. Syphilitic affections of the eighth nerve, with a still negative Wassermann reaction in the earliest stage of lues, are in analogy with those cases in which clinically a late, a luetic labyrinthine affection is practically undoubted, whose blood reaction is negative, and which in part are nevertheless improved by specific treatment. Comparative investigations have shown that the cochlear nerve has a greater tendency to improvement under Hg and salvarsan treatment, whereas the vestibular nerve apparently tends to aggravation, but this is probably more frequently due to retrolabyrinthine changes.

Inquiries made several months after the termination of the treatment yielded no uniform result in the sense, for example, that aggravations noted during the treatment in one of the branches of the eighth nerve continued to become worse. It is noteworthy that many patients complained of disturbances suggestive of mild cerebral syphilis, and the possibility of such an outcome after distinct aggravation of one of the two branches of the eighth nerve during the treatment should be kept in mind. In view of the frequency of involvement of the eighth nerve, a systematic control of all such cases after the completion of treatment is not practicable. Perhaps a further control may be based on the findings in the spinal puncture fluid at the end of the treatment, in case the factor of distinct aggravation of the condition of the eighth nerve should prove to possess prognostic importance for the eventuation of cerebral syphilis.



**Tuberculosis and Abortive Treatment of Syphilis.**—Tieche. *Schweizerische medizinische Wochenschrift*, 1920, No. 8, p. 149.

The author calls attention to certain dangers involved in the treatment of patients suffering from the double infection of tuberculosis and syphilis. The actual existence of such danger results clearly from his experience in the Lausanne Polyclinic, where in a material of 150 to 200 patients yearly, disturbances were regularly noted which had to be interpreted as suggestive of tuberculosis or even as acute manifestations of tuberculosis. The question arises: How do mercury and neosalvarsan act upon the organism in the presence of clinically demonstrable tubercular foci, and how do patients having latent tuberculosis tolerate energetic treatment with these preparations? Does this treatment favor the progress of an already manifest tuberculosis, and does it arouse closed latent foci to renewed activity? In the author's material, syphilis alone was never found to create a territory for the distribution of tuberculosis, but the tuberculosis invariably manifested itself in the course of the treatment, usually not until after a very energetic course of treatment. In patients having primary syphilis, who are subjected to abortive treatment, the organism can hardly have been damaged by the syphilis, as the bulk of the pathogenic agents is destroyed before they can do harm. Nevertheless, an existing pulmonary tuberculosis becomes worse, or a latent tuberculosis becomes active, suggesting that the principal danger may be referable to incautious treatment, which creates the soil for the distribution of the tuberculosis. When a disposition to tuberculosis is explained by an impairment of the biologic chemical adjustment of the body against the pathogenic agent, it is readily understood that the two disturbing components such as mercury and neosalvarsan may occasionally upset the complicated system of forces which still maintain the balance so that the fight is decided in favor of the tubercle bacilli. This radical chemical therapeutic procedure perhaps temporarily interferes with the production of antibodies, thereby opening a wide entrance avenue to the distribution of the tubercle bacilli. The author does not mean to exaggerate the danger of combined mercury and salvarsan treatment in patients having latent tuberculosis. Many tuberculous individuals readily tolerate such combined treatments. Under no circumstances, however, should a cure of syphilis with abortive treatment be enforced at the expense of the tuberculosis. How much may be ventured, in case an abortive success is still to be expected, depends principally upon the toleration of the specific preparations and the character of the pulmonary or other tuberculosis. It should always be remembered that the syphilis is still accessible to later treatment, whereas tuberculosis, when it has once become progressive, has an extremely unfavorable prognosis. A series of observers, with whom the author is obliged to agree, regard a recent syphilitic infection as less responsible for the progressiveness of an existing tuberculosis than the institution of antiluetic treatment.



**Meta-luetic Tuberculous Mixed Infection.**—K. Zehner. *Schweizerische Medizinische Wochenschrift*, 1920, No. 30, p. 651.

The relations between two pronounced infectious diseases, as frequently manifested in the combination of lues and tuberculosis, are not yet sufficiently understood, and the author reports an instructive case, illustrating the pathogenesis, course, diagnosis, and treatment of this chronic mixed infection. The patient, a man fifty years of age, gave a family history free from lues and tuberculosis. At the age of seventeen years, he acquired a luetic infection and soon afterwards suffered from papules of the buccal mucosa (secondary lues) which disappeared after two mercurial inunction cures. One year later he underwent another inunction cure and after two years was given Hg intramuscularly. Since his thirty-sixth year he has suffered repeatedly from nasopharyngeal catarrh and especially from chronic bronchitis, possibly of specific character. In his fortieth year, he was treated for chronic laryngitis (vegetative infiltration of arytenoid cartilage), at first with nonspecific remedies. No cure resulting, luetic phenomena were suspected, but no specific treatment was instituted until two years later. At this time, two intramuscular neosalvarsan injections were administered in the vicinity of the right sciatic nerve, combined with Hg treatment. At the end of a year, the laryngitis had entirely subsided. In 1916, the patient's general condition became worse, with extreme nervousness, emaciation, and psychic depression. In 1917, he complained of very severe neuralgic pains in the right calf, which were interpreted as sciatica. Loss of weight and aggravation of bronchitis. Left-sided pulmonary tuberculosis was now demonstrated for the first time and soon extended to the right lung, in the presence of a high temperature. A course of tuberculin treatment was instituted, leading to subjective and objective improvement, with a subfebrile temperature and disappearance of positive bacillary findings in the sputum. Nervous sensations of variable degree still persisted, especially in the region of the diaphragm, and soon afterwards the expectoration returned. Examination for tubercle bacilli proved negative. Findings on x-ray examination likewise contradicted the physical pulmonary findings which simulated destructive processes in the upper lobes. A very important factor was represented by the peculiar pains in the upper abdominal region, the lumbar region, and the right leg; which had hitherto been interpreted as ordinary neuralgias. Trophoneurotic sequelæ were altogether absent, although the patient had been bed-ridden for nearly two years.

The cause of this peculiar condition remained obscure until the luetic infection of thirty-four years ago was taken into consideration. The correctness of this assumption was shown by the brilliant therapeutic effect obtained by means of antiluetic treatment. This case was evidently one of meta-lues, becoming manifest through pulmonary tuberculosis and flourishing also after the subsidence of tuberculous advance. The secondary lues, expressed by the papules of the buccal mucosa and the laryngeal affection, was rendered latent through the specific mercury and salvarsan treatment, until meta-luetic complications were started as the result of mobilization by pulmonary tuberculosis. In a general way, the prognosis is aggravated in this chronic mixed infection,

especially as regards the tuberculous component; but in this remarkable case, the arrested tuberculosis elicited the lues and maintained its activity. The accuracy of the diagnosis in cases of this kind is confirmed exclusively by the therapeutic effect of antiluetic treatment, which may yield remarkable results even in badly neglected cases, or in the meta-luetic stage, as in the present observation.

**Primary Syphilitic Icterus.**—G. Milian. *Paris Médical*, 1920, No. 34, p. 141.

Whereas secondary syphilitic icterus, of the benign or severe type, has long been known, icterus has not apparently been described as a concomitant of the chancre, in the form of primary syphilitic icterus. The author is enabled to contribute three illustrative observations, which moreover show the peculiar affinity of the treponema for the liver, frequently observed in congenitally syphilitic infants. The patients were a woman of twenty-one years and two men of twenty-seven and thirty-eight years, respectively, who undoubtedly presented a primary syphilitic icterus, meaning syphilitic icterus coincident with the chancre, antedating the roseola. The icterus appears a few days after, or together with, or even two or three days before the chancre, without special general phenomena, without digestive disturbances; only in one instance slight vomiting was noted. The tongue is moist, not coated, perhaps sometimes rather white. The liver is slightly increased in size, likewise the spleen; the urine contains bile; the feces are discolored in proportion to the severity of the icterus. Neither albumen nor sugar are found in the urine. Fever is absent at the onset, but the temperature rises somewhat when the Wassermann reaction becomes positive. There is general fatigue, anorexia, and some tenderness of the liver on palpation of the epigastric fossa. It is noteworthy that the icterus manifests itself before the Wassermann reaction is positive. It may even subside before the appearance of the latter. As a rule it runs a rapid course. It may undergo a spontaneous cure through a simple milk-diet, approximately following the course of the chancre and healing at the same time. The duration in the author's three cases was twelve days, twenty-two days, and twenty-seven days, respectively. In the last two cases, the icterus became associated with roseola, and the cure of the icterus was obtained by means of specific treatment at the same time as the other syphilitic manifestations. In one case, the icterus after its subsidence reappeared during forty-eight hours, on application of treatment in the form of intravenous injections of Hg cyanide. Pruritus was not observed in any of these cases of primary icterus, and in the author's experience is usually absent in luetic icterus. It is noteworthy that the Wassermann serum reaction does not become positive until the time of its normal appearance with the chancre, so that the icterus is evidently incapable of giving rise to a positive Wassermann reaction. These cases of primary syphilitic icterus concerned especially patients suffering from a rather obstinate lues, usually with Herxheimer's reaction.

The reasons why this icterus, appearing at the same time as the chancre, is to be interpreted as luetic in character, are aside from the coincidence, into



parallel development with the chancre, the tendency to spontaneous cure like the chancre, the absence of other demonstrable cause of icterus, more particularly nothing suggestive of catarrhal icterus, fever being absent and the digestive tract practically normal. A theoretic objection to the possibility of primary syphilitic icterus does not exist. It has been shown that already at the onset of the chancre, treponemas are in circulation and may lodge at some point in the body, giving rise to visceral manifestations. This premature distribution of the treponema in the body has been shown by Hoffman's inoculation of monkeys, which proved that the blood of syphilitics, while it contains only a small amount of virus, is already contagious forty days after the infection, although three or four weeks must still be allowed to elapse before the roseola makes its appearance.

**The Mental Troubles of Syphilitics.**—Barbé, Paris. *La Presse Médicale*, July 7, 1920, vol. xxviii, No. 46.

The rôle of syphilis in the production of psychotic states is very elusive and difficult to delimit. Before we reach the subject proper we have to bear in mind so-called syphilophobias and syphilomanias, in which the virus of the disease is not a factor at all. Suicide by syphilitics cannot be straightway set down as due to the virus. In considering the pure subject we begin naturally with the secondary stage and here mental aberration may sometimes be traced to the severe headache and other forms of pain with the resulting insomnia over and above the possibility of toxic action on the cortex and of lesions in the same area. Nonspecific toxi-infectious insanity of syphilitic origin during the secondary period is familiar in literature, the fundamental symptoms being obtusion, hebetude and torpor. The syphilitic psychoses of the tertiary period due chiefly to meningoencephalitis and vascular disease are well known and understood. But over and above these are psychoses due to ordinary gummatous syphilis of the brain—not metasymphilis—which comprise three forms known as pseudodemential or confusional, periodical with exaltation or depression and paranoid, with or without systematized delusions of persecution. The author considers these three forms *in extenso* because of the great difficulty in diagnosis, which involves the exclusion of a great variety of psychotic states. The mere history of syphilis and positive Wassermann may not indicate the syphilitic motivation of the psychosis. One of the most difficult tasks is to discriminate between ordinary syphilis and paresis and only a careful comparison of clinical and laboratory finds may solve the problem. The article concludes with an account of the psychoses seen in the heredosyphilitic.

**Cardio-aortic Syphilis of Thirty-five Years' Duration.**—Clark, Rio de Janeiro. *Brazil-Medico*, June 19, 1920, vol. xxxiv, No. 25.

The patient was 59 years of age, admitted to the clinic for intermittent fever. He had contracted syphilis in 1882, or 38 years before the consultation. When the infection was in its fourth year he began to suffer from cardiac attacks—palpitation and tachycardia—in which a certain type was evident.



This type has since persisted so that the paroxysmal tachycardia which the author detected was apparently identical with the first paroxysms. Aside from the history of syphilis the anamnesis was negative. Physical examination revealed an indubitable aortic insufficiency, the left ventricle being but slightly enlarged with the apex 12 cm. from the median line in the fifth interspace. The radioscopic examination showed a slight dilatation of the aorta not sufficient to be termed aneurysmal. The pulse outside of the paroxysms was a true Corrigan, regular, slow and about 60. The tension was 180-100. No pretabes. The urine showed only some water retention, not unusual phenomenon in old syphilitics. The Wassermann was a four-plus while the examination of the spinal fluid was negative. The case is remarkable when we bear in mind that cardioaortic syphilis has an excessively bad prognosis and usually means death within a short period.

**Cardiac Syphilis and Its Treatment.**—Leredde, Paris. *Bulletin de la Société Française de Dermatologie et de Syphiligraphie*, 1920, No. 3.

The author, after giving credit to Warthin for his pioneer researches in this department, reports 15 miscellaneous cases of cardiac syphilis. The first phenomenon taken up is morning arrhythmia which accompanies either tachy- or bradycardia and often subsides after salvarsan. Generally speaking morning pulse troubles may be seen in the secondary stage of the disease, but are more apt to be seen in old syphilis when presumably organic disease is present. Of five cases of pulse troubles given but one was in the secondary period. Salvarsan is able to regulate arrhythmis and slow or hasten the pulse when abnormally fast or slow, but the amounts of salvarsan given in these cases before the results are obtained seem very great, although well borne. Naturally the treatment is not directed primarily against the cardiac behavior and in the course of indicated treatment this improvement in the cardiac action has been noted as a by-product so to speak. In certain cases the seroreaction was negative, and the heart was apparently sound. Treatment was apparently pushed to avert metasyphilis. In such cases salvarsan appeared to produce tachycardia and other anomalies of the pulse but these subsided without discontinuing the remedy. The author mentions in detail a case of bradycardic reaction. In the same patient there was also a marked Herxheimer reaction. Rules are laid down for the treatment of these cases, and especially for the recognition and treatment of early cardiac involvement. In old cardiac cases in which salvarsan is usually contraindicated in the opinion of many authorities Leredde insists that with a definite and suitable technic salvarsan is the remedy, using all care and precaution. The aim and the only aim is sterilization.

**Sciatic Neuralgia of Syphilitic Origin.**—Boudet (Paris). *Gazette des Hôpitaux*, May 18-20, 1920, vol. xciii, No. 46.

As a result of the war the literature of sciatic neuralgias has been greatly augmented. Many papers have been devoted to the exposure of simulation. In undoubted cases the resistance to treatment is often extreme and hence we

are justified in seeking out especially measures of causal therapeutics such as antisyphilitic regimen. A sciatica of syphilitic origin has been known since the XVIII century. Nevertheless it must be confessed that the number of recorded cases is not large or rather was not large up to the time of serodiagnosis. In 1884 Dubois was able to find but 20 cases. The present author has attacked the problem in a special fashion. He accumulated notes of 150 cases of medical sciatica in which traumatism and psychogenic motivation could alike be excluded and tested the subjects for the seroreaction. A positive Wassermann was obtained in 58, or 38.66 per cent. In 12 of these only was syphilis admitted and in 10 others there were collateral evidences or stigmata which pointed to syphilis. This leaves 36 with no evidence of the disease beyond the Wassermann. The patients were all soldiers and the determining causation of the disease was presumably exposure in the trenches and other occupational factors. After a course of 10 injections of mercury cyanate the soldiers were enabled to rejoin their commands. The average age of the men was 36 and the syphilis was from 7 to 10 years old. The poverty of direct evidences of syphilis led the author to a study of the spinal fluid. The subject as a rule is not likely to consent to spinal puncture unless this is a necessity. In one case the finds were glucose, albumin 0.35 gm., no leucocytosis and Noguchi negative. One subject showed incipient tabes and with sciatica were seen the fulgurating pains of the former. The mercurial injections were intravenous.

**Vascular Syphilis.**—Etienne, Nancy. *La Presse Médicale*, May 29, 1920, vol. xxviii, No. 35.

In simple aortitis of the thoracic aorta syphilis is present in 80 to 85 per cent. Aortitis in all its forms is frequent in syphilitics including tabetics. Aortitis in the very young including the fetus and newborn is due to heredo-syphilis in about half the cases. What is said of the thoracic aorta applies equally to the abdominal although abdominal aortitis is often only an extension of the disease downward. Valvular lesions of the aortic valves may be associated with aortitis and the suprasigmoid segment of the arch is the favorite point of attack in aortitis. We may see stenosis or incompetence of the valves. The mitral valves are often secondarily attacked. In cases of intact valves we sometimes see functional insufficiency of the aorta from dilatation—so-called Hodgson's disease. Suprasigmoid aortitis of syphilitic origin may involve the coronaries, either the orifices alone, the trunks of the vessels or the myocardium. There then develops ventricular insufficiency and angina pectoris which often responds surprisingly well to specific treatment. Another syndrome is acute leftsided asystole with acute pulmonary edema. In general whenever rheumatism can be excluded in cardiovascular disease the treatment of syphilis should be pushed. This paper was discussed by Milian who mentioned a specific tachycardia seen during the secondary period. There is a very characteristic syndrome of tachycardia, arrhythmia, hypertension, absence of murmurs, etc. The treatment makes the diagnosis and the essence of the malady is probably a myocarditis limited to the fibers of His. Wybauw and Desneux find that arsenic properly used is the remedy of choice in the

treatment of syphilitic vascular disease. Gastou discussed the subject of radiography in syphilitic cardiovascular disease which is of great value aside from its demonstration of aneurysm. Differentiation may be possible between aneurysm, mediastinal tumors, mediastinal adenitis, tuberculosis of the mediastinum, etc.

**Syphilis, Tuberculosis, and Cancer of the Rectum.**—C. Milton Linthicum, Baltimore. *American Journal of Surgery*, 1920, vol. xxxvi, p. 47.

The three diseases can be recognized early and differentiated. Tuberculosis is rarely a primary disease of the rectum; it occurs late secondarily and its cure is exceptional. Syphilis occurs as a syphilide or gumma, its early constitutional treatment prevents complications and is curative. Cancer occurring in the rectum can be seen in 65 per cent of intestinal cancers by the sigmoidoscope, and its early removal is the only hope for successful treatment.

**A Case of Vascular Syphilis.**—A. E. Kuhlmann, U.S.N., and C. C. Ammerman, U.S.N.R.F. *United States Naval Medical Bulletin*, 1920, vol. xiv, p. 245.

The items of particular interest in the case are: (1) That the processes of the disease were apparently little, if at all delayed or prevented by the administration of all antiluetics; (2) that a person with the pathologic condition shown at autopsy could have been apparently well and without symptoms or signs until about 72 hours before death.

**Syphilitic Spondylitis.**—S. C. Evans and C. F. Marshall. *Lancet*, London, 1920, vol. cxcviii, p. 656.

Noteworthy features of this case are the rarity of the lesion, its occurrence in spite of treatment, and the persistently negative Wassermann reaction, the first test being made when the vertebral lesions were in active development. All tests were made at reliable institutions, the first and second in Government laboratories in India and the third in a well-known London hospital. This case would therefore appear to serve as a warning against placing too much reliance on the Wassermann reaction, both as regards diagnosis and prognosis.

**Syphilis and Pregnancy.**—William J. Young, Louisville, Ky. *Surgery, Gynecology and Obstetrics*, 1920, vol. xxx, p. 508.

Routine Wassermann examination should be made in obstetric wards of charity institutions when patients are admitted. It should be just as much the duty of the obstetrician to ascertain evidence or history of lues in his patient as to conduct delivery. Considering the source of patients in the charity institutions the percentage of syphilis associated with pregnancy (in Louisville) is not excessive.

**Oral Syphilis.**—Herman Goodman, New York. *Dental Cosmos*, 1920, vol. xii, p. 591.

Syphilis is frequently expressed by lesions about the oral cavity. These lesions of the different stages of the disease are protean in character, that is,



take various forms. The dentist should be observant of the oral cavity of each client, in order to avoid infection, and to avoid carrying the infection to other patients. Bacterial investigation of suspicious lesions about the mouth are especially interesting because of the necessity of differentiating the non-pathogenic spiral organisms which are normally present and which simulate the *Spirochaeta pallida*, the causative agent of syphilis. The syphilitic lesions of the mouth are part of the general infection. The lesions here are pathologically the same as elsewhere in the body, modified by the special conditions of heat and moisture of the oral cavity and the presence of other bacteria. The mucous patch, one of the most dangerous and persistent lesions of the disease, is present in about 50 per cent of all secondary syphilitics. The perforations of the hard palate, due to ulcerations of gumma of the part, are frequently found in late syphilitics. This destruction is not remedied by anti-syphilitic treatment. The congenital syphilitic presents many lesions of the mouth. The stigmata and dystrophies of the teeth are of especial interest. They are frequent, permanent, characteristic, and diagnostic of the condition. The dentist should observe rigid asepsis. He should take all reasonable precautions, and use more than ordinary methods of sterilization of instruments and hands during his examinations and operative procedures. In all certain or suspicious cases, the patient should be advised to apply to his family physician, and the dentist should delay his work, if possible, until assured that the patient is noninfectious.

**Gastric Syphilis with the Report of a Case.**—H. D. McGaughey and James I. Tyree, Joplin, Mo. *Journal of the Missouri State Medical Association*, 1920, vol. xvii, p. 21.

The basis of diagnosis of gastric syphilis is: 1. Patient giving symptoms of malignancy but under cancer age. 2. Cachexia not in keeping with reduced red cell count. 3. Symptoms not painful enough for ordinary peptic ulcer. 4. One child with congenital syphilis, five miscarriages. 5. Positive Wassermann. 6. Blood cells and mucus in feces. 7. Roentgenologic findings, filling defect with absence of adhesions indicative of an organic lesion. 8. Therapeutic test, after six weeks' antisyphilitic treatment patient's bowel movements have been reduced to two daily.

**Specific Aortitis.**—William D. Reid, Boston. *Boston Medical and Surgical Journal*, 1920, vol. clxxxiii, p. 105.

Syphilitic disease of the aorta is one of the most common and most serious findings in all cases of acquired syphilis. The lesion is essentially a mesaortitis, and a manifestation of active syphilitic disease; its conception as a parasymphilide being made untenable by the discovery in 1906 of the spirochete directly in the aortic lesion. The aortic process frequently extends to the aortic cusps, and Warthin has shown that relatively often there is an accompanying myocarditis of spirochetel origin. Aortic roughening, aortic regurgitation, dilatation or aneurysm of the aortic arch, and angina pectoris are common in syphilitic aortitis. Aortic or mitral stenosis is of exceptional occurrence in

connection with specific aortitis. Nonsyphilitic forms of aortitis are rare. Many cases may be called latent in that symptoms are absent. Such cases are commonly undiagnosed until disclosed, perhaps, in a routine roentgen examination. There is no one point on which a diagnosis should be based, but only after a study of all the facts in a given case should a decision be rendered. Every case of cardiac disturbance of obscure origin, especially if the patient be a young adult and if there are signs of involvement of the aortic valve, should promptly suggest the probability of syphilitic causation. A positive Wassermann reaction is of confirmatory value but is frequently absent. Roentgen examination, though unreliable in early cases, gives perhaps the most reliable findings. Specific aortitis evidences a tendency to progressive impairment of the heart and aorta and is, therefore, of serious import. Treatment should be directed primarily towards killing the spirochetes in the aortic lesions. Decomposition of the heart is to be treated as in that of nonsyphilitic origin. Early diagnosis is imperative. The author feels that there should be a greater willingness on the part of clinicians to make a tentative diagnosis of specific aortitis, and a resort to a therapeutic test. Along such lines lies our greatest hope of improvement in the mortality rate of this disease.

**The Wassermann Reaction and Miscarriages.**—Herman Goodman, New York. *Surgery, Gynecology and Obstetrics*, 1920, vol. xxx, p. 368.

The author found that among 1,320 pregnant women, 87 per cent were Wassermann negative. Only 6.7 per cent gave a four-plus positive reaction, and in two per cent more of the cases, the Wassermann was three-plus positive. Of the Wassermann negative multipara, 37 per cent had suffered one or more miscarriages as compared to 52 per cent of the four-plus positive cases. Only one woman among the 1,320 gave a history of having been known to be infected with syphilis, although approximately one woman out of each 11 gave a strongly positive Wassermann reaction, indicating in all probability, a syphilitic infection. In perhaps every instance, the husband was responsible for the disease in the wife. And yet, there are hospitals throughout the land that refuse to admit men suffering with syphilis. "As they sow, so shall they reap" is the attitude of the hospital board. The diseased wife, and the unborn syphilitic offspring is the result. Every case of syphilis may become the center of an ever-widening circle of infection.

**Cerebral Syphilis of the Manic-Depressive Type.**—L. Guedes, *Archivos Rio-Grandenses de Medicina*, 1920, No. 1, p. 19.

The variegated clinical forms of cerebral syphilis include a manic-depressive type, characterized by phenomena of depression or excitement, paranoid delirium, multiple hallucinations, catatonic states, and so forth, associated with emotional disturbances, and therefore closely simulating dementia precox, so that it is sometimes impossible to render a correct diagnosis without prolonged observation or the valuable assistance of the laboratory. A patient recently observed by the author, a white Brazilian merchant thirty-six years of age, presented the distinct picture of dementia precox, but this diagnosis

was not unconditionally accepted at the time of his admission to the San Pedro Hospital. Keeping in mind the possibility of cerebral syphilis, certain laboratory tests were resorted to, with the result that the four Nonne reactions all proved positive (Wassermann reaction in the blood, positive, in the cerebrospinal fluid, positive, moderate lymphocytosis and hyperalbumosis). These findings threw light upon the condition, which was now recognized as due to cerebral syphilis of the manic-depressive type. Consequently a course of specific treatment was prescribed and was carried out in the patient's home, in the form of small progressively increasing injections of neosalvarsan, mercurial and sodium iodide injections, in progressive doses. At the end of about three months, the patient's condition was markedly better and continued to improve from day to day, so that he became enabled to resume the management of his business. The therapeutic indications in similar cases evidently depend upon the accurate diagnosis, and the beneficial results in the above described case show the necessity of always being on guard against syphilis, an insidious infection with multiple misleading manifestations.

**Observations on Three Cases of Deafness Due to Congenital Syphilis.**—C. Hennebert. *Archivio Italiano di Otologia, Rinologia e Laringologia*, 1920, vol. xxxi, No. 3, p. 198.

The observations in the first two cases constitute the classical picture of hereditary luetic labyrinthitis, as described by the author in an entire series of communications to the Belgian and French Oto-rhino-laryngological Societies. Since 1905, the date when the name of Hennebert's syndrome was first applied to the symptom-complex of these cases, he has been enabled to examine twenty-five patients and on the basis of his observations wishes to emphasize the following points: The onset of the deafness in the first case dated back to early infancy, in the second to the age of fifteen years. The luetic legacy may be presented at a much later date, in the twenties or thirties, as in a case of the author's concerning a patient thirty-six years of age. This point must be emphasized, because one might hesitate to attribute functional disturbances supervening at such an advanced age to congenital syphilis, if typical examples had not been recorded. Ocular lesions, the traces of old parenchymatous keratitis, were present in the last two patients, as in the great majority of all cases. The eye affections invariably precede, sometimes by many years, the manifestations on the part of the ear. Hearing was relatively slightly impaired in the first patient, who still heard whispered speech from near by on one side, but was much more seriously interfered with in the second patient, who perceived ordinary conversational speech only at a distance of 25 cm. The variability of the deafness, between certain limits, from one day to another, has been noted, due to the influence of treatment or sometimes without a known cause. As a rule the deafness is very pronounced, in ten of twenty-two cases the hearing capacity was lost in both ears, eight times it was lost in only one ear.

In the great majority of the cases, the special syndrome of labyrinthitis due to congenital syphilis may be formulated as follows: Pneumatic test, posi-



tive, rotatory test, negative, thermic test, greatly diminished. The several parts of this vestibular triad may present differences in degree, within certain limits, varying in different combinations according to the cases.

The third patient recently observed by the author was a boy about eight years of age, who presented auditory disturbances of a rapidly progressive character, leading in two months to total deafness. This boy showed undeniable stigmata of congenital syphilis, an enormous swelling of one knee, articular deformities of the fingers of both hands, and so forth. The Bordet-Wassermann reaction was negative. The vestibular examination in this patient showed, by the normal thermic nystagmus on both sides, that the vestibules were intact, and the deafness might have been attributed to a central lesion, with an unchanged cochlea, in view of the established intactness of both vestibules. At the present state of knowledge, there is no way of rendering in such cases a differential diagnosis between deafness due to a functional destruction of the entire cochlea and deafness due to deep lesions of the acoustic tracts.

**Syphilis Simulating Typhoid Fever.**—G. Laurenti. *Rivista Ospedaliera; Giornale di Medicina e Chirurgia*, 1920, vol. x, No. 3, p. 92.

It is a well-established fact that syphilis is frequently accompanied by fever, which may appear under the three different forms of intermittent, continuous, and atypical fever. The continuous type is less common than the others, and its interpretation is difficult in most of the cases. It is more frequently observed in women than in men, and is apt to be met with in the secondary period of syphilis; presumably because the luetic infection is often overlooked in women, at least in the beginning, and because it has had time to become generalized, whereas circumscribed visceral localizations in other stages more frequently are suggestive of tuberculosis or malaria. Patients with syphilis simulating typhoid fever are often in a state of marked prostration and nearly continuous somnolence, and many complain of persistent headache. These symptoms are associated with diffuse pains in the spine and the limbs, usually worse at night, like the headache. In certain particulars, the clinical picture slightly differs from the ordinary symptomatology of typhoid infections. The eye does not show the stuporous condition commonly seen in typhoid fever, and the tongue is not so dry, according to Morini, but in the author's and in Perrin's experience, the tongue closely resembled the typhoid tongue. The skin is warm, but not dry and burning. Epistaxis and pronounced abdominal symptoms are not common, according to Morini. In the author's case, however, there were well-marked persistent meteorism and frequent attacks of diarrhea; the same observations were made by Perrin. The diagnosis is not easy, as the condition must be differentiated from all eruptive fevers in the precursive stage when the patient is seen during the first few days, from typhoid and paratyphoid infections, from septicemia, and so forth. The only reliable diagnostic guides consist in the presence of spirochetes in the cutaneous or mucous lesions, the Wassermann reaction; and the prolonged persistence of a negative agglutination-phenomena for the Eberth

bacillus. All the other more or less typical symptoms must be very cautiously estimated, as not specific for a luetic infection. Thus the temperature curve, the dissociation of pulse and temperature, the absence of a dicrotic pulse, the presence of obstinate headache, more or less typical eruptions, all of these are suggestive signs which should arouse suspicion but do not suffice for a positive diagnosis. This can be rendered only in the presence of one or more of the three essential signs mentioned above, keeping in mind that a syphilitic patient may have a typhoid infection (positive Wassermann and positive Widal) and that agglutination may be retarded in a case of typhoid fever.

A typical case of luetic fever of typhoid type recently came under the author's observation, concerning a woman 28 years of age, who complained of severe persistent frontal headache and diffuse bony pains with nocturnal exacerbations. There was a high temperature and a rather soft pulse of moderate frequency and tension. Two important symptoms were diarrhea and meteorism, and the appearance of numerous suspicious macules on the abdomen. The Widal test proved negative, and examination of the blood for malaria proved likewise negative. In the performance of spinal puncture, a few sharply outlined eruptions covered with a whitish exudate were noted in the peri-anal region, and in view of the importance of these findings, two centigrams of bichloride of mercury were injected by the venous route. After a few hours, the temperature diminished slightly and the curve began to show distinct fluctuations. On the next day, another injection of bichloride of mercury was administered, with an equally beneficial effect upon the temperature. Numerous macules made their appearance also on the anterior aspect of the thighs, not vanishing on pressure. The laboratory report showed a completely positive Wassermann reaction. Further treatment with novarsenobenzol billon by the venous route in progressive doses, combined with mercury, resulted in complete recovery, with subsidence of all visible manifestations of lues within a short time.

**Meinicke's Reaction in the Diagnosis of Syphilis.**—Editorial in *La Riforma Medica*, June 12, 1920, vol. xxxvi, 24.

During the period 1908-1916 of the serology of syphilis we had to do with flocculent precipitates. The author enumerates the procedures of Klausner, Porges and Meyer, Neubauer, Elias and Salomon, Hermann and Perutz and Landsteiner and Paul. Despite the theoretic value of the principles involved none of these modifications of the seroreaction have been introduced into routine practice. During the past three years two new methods have been introduced—those of Sachs and Georgi and of Meinicke,—which have proved to be of practical value. What is known as the third modification of the Meinicke reaction has been used in over 2000 cases at The Franz-Joseph and Rudolf Hospital, Vienna, parallel with the Wassermann, either with alcoholic extract or the emulsion of the extract. Beef heart was extracted with alcohol for 72 hours and the clear fluid was placed in the thermostat at 37° C. for 24 hours. Emulsion of extract was made with 2 per cent NaCl. In the

reaction four parts of emulsion and 1 of serum were used and the reaction was apparent after 24 hours in the thermostat. The agglutinoscope of Kuhn and Wojtke was used and for a positive reaction it is only necessary to see in the dark room with artificial oblique light and slight magnification with a lens a fine flocculence or granulation. In nearly 95 per cent of cases the results agreed with those of the Wassermann. If the Wassermann is negative or incomplete with alcoholic extract and positive with emulsion of extract and if at the same time the Meinicke reaction is positive then the reaction should be regarded as positive. If both types of Wassermann are negative and the Meinicke is positive the reaction should also be declared positive.

**Differential Diagnosis of Tuberculosis and Syphilis.**—Theodore Zbinden, Toledo. *Ohio State Medical Journal*, 1920, vol. xvi, p. 251.

The distinction between tuberculosis and syphilis is a daily problem for every physician and often presents great difficulties. The two diseases are remarkably similar as to pathology and clinical course. Syphilis produces milder symptoms than tuberculosis, but it is also more treacherous. It is rarely attended by fever, whereas the opposite is true of tuberculosis. Syphilis may destroy large portions of the body, yet often heals completely with the formation of large scars. Extensive tuberculosis is rarely arrested, unless surgical removal is possible. Physical examination alone is not reliable. Examination for the tubercle bacillus is applicable in possibly one-half the cases, and is conclusive in less than one-fourth. The skin tuberculin reactions are of value, but are conclusive only in the very young. In people past fifteen they are valuable only in 10 per cent of cases. The hypodermic test is difficult and dangerous, yet very accurate. The Wassermann reaction is really a necessity for proper diagnosis but discloses only two-thirds of the cases having syphilis. Roentgen-ray examination is of great value in the hands of an expert; it explains the phenomena observed by physical diagnosis, but gives much more information of value. The therapeutic test has decided limitations.

**Differential Diagnosis Between the Pains of Tabes Dorsalis and Those of Focal Infection.**—Albert M. Crance, Bay City, Mich. *Medical Record*, 1920, vol. xevii, 606.

This case is presented to illustrate the importance of a more careful consideration of focal infection. This patient's condition had several times previously been diagnosed as tabes dorsalis, and on none of the occasions had focal infection been considered as a possibility in its etiology.

**Frambesia Tropica (Yaws) a Study of the Literature with Personal Observations, a Critique of Its Supposed Identity with Syphilis, and a Bibliography.**—Herman Goodman, *Archives of Dermatology and Syphilology*, n. s. 1, 7, July, 1920.

The identity of syphilis and yaws has been affirmed and denied innumerable times. Prior to the discoveries in bacteriology and serology of this cen-



tury, scientific gentlemen in different parts of the tropical world amassed a huge fund of clinical differentiation. The accompanying table from Jeanselme and Rist gives many of the points that lead most observers to maintain the dual character of these diseases:

Comparison between syphilis and Frambesia Tropica

SYPHILIS

1. Disease pandemic.
2. Acquired by heredity and contagion.
3. Begins by a primary pathognomonic lesion at point of inoculation.
4. Immunity conferred by syphilis is in a sense permanent.
5. All attempts at autoinoculation of a patient with secondary or tertiary syphilis are fruitless.
6. The hard chancre and other signs of syphilis can appear on a subject who may have yaws.
7. The polymorphism of syphilitic manifestations.
8. Syphilides, at least those of the tertiary period destroy the skin, and leave after cure, permanent scars.
9. Syphilis is an infection in which the several lesions correspond to three periods, primary, secondary, and tertiary.
10. Syphilitic eruptions involve the mucous membranes.
11. Localizations in the viscera.
12. Syphilides are not pruriginous.
13. Alopecia in secondary period.

FRAMBESIA TROPICA

1. Disease tropical.
2. Acquired only by contagion.
3. Initial lesion near portal of entry is not constant nor different from lesions appearing later.
4. Reinoculation of yaws is possible.
5. The autoinoculation of yaws is possible for an indefinite period, but quite long.
6. Yaws can develop on a subject with syphilis.
7. Monotony of eruption; it showing only papilloma.
8. Frambesial lesion which is not exposed to any irritation heals without leaving a trace.
9. All the manifestations of yaws are identical, whatever be their date.
10. Frambesia lesions do not involve mucous membranes.
11. No localization in the viscera.
12. Yaw lesions are accompanied by lively itching.
13. No alopecia in course of the disease.

Manson mentions the following points of contrast in the clinical features of the two diseases, all of which are lacking in *frambesia tropica*: primary sore; infection of the fetus; adenitis; exanthem; alopecia; absence of pruritis; iritis; affection of the permanent teeth; bone and eye affections; congenital lesions; polymorphism of the eruption; nerve lesions and gummas of syphilis. Moreover both these diseases may occur in the same individual.

Macleod in a histologic examination gives this summary which suggests that *frambesia tropica* and syphilis are different histologic entities.

(a) Cellular infiltration. The plasma cells are not so definitely clustered around the vessels in yaws, as they are in syphilis, nor do they form foci sug-

gesting a tuberculous nodule, as they occasionally do in the latter disease. They are seldom arranged in rows, which frequently occurs in syphilis. Large multinuclear cells (chorioplques) and true giant cells which may be present in syphilis are absent. No hyaline degeneration, such as may be found in syphilis, is detected in the plasma cells.

(b) Fibrous stroma. The rarefaction of the collagen is more marked in yaws than in syphilis; organization is not detected, and colloid degeneration such as occurs in syphilitic gumma is absent.

(c) Blood vessels. There is no tendency to thickening of the vessel wall or to endothelial proliferation, such as so frequently pertains in syphilis.

(d) Epithelium. The proliferation changes in the epidermis in yaws are only equaled in syphilis in the condylomata, while the marked tendency of the stratum corneum (hyperkeratosis), which is an invariable characteristic in yaws, is unusual in syphilis.

Maul from a roentgen ray examination of twenty cases notes:

That with the exception of 2 per cent of cases showing as a swelling over the surface of bone, the roentgen ray picture is different from the bone lesion of syphilis in that:

(1) The periosteal infiltration is absent.

(2) The thickening of the cortex of the bone is absent. Also in the 2 per cent of cases where thickening of the cortex is present, the thickening remains localized, does not extend along the whole length of the bone, and sooner or later shows rarefaction in the center of the bone.

The radiogram can be used as an additional means of differentiating yaws from syphilis, where there is involvement of the bones, and is a confirmation of the evidence that the two diseases are distinct.

Diagnosis by therapeutic agents in the case of mercury may be of aid, since mercury has little if any effect on the lesions of frambesia. The results of specific chemotherapy are equally good in syphilis and yaws, although it is maintained that the latter disease proves more amenable to arsphenamine.

The demonstration almost simultaneously, of the causative organism in both diseases did not furnish conclusive ground for differentiation. The spirochetes, pallida and pertenuis, are morphologically identical and biologically very similar. However, the following differences in experimental infection of frambesia tropica compared with syphilis have been noted by Nichols:

Incubation period for testicular lesion is eight days shorter and for skin lesions it is twenty days shorter (in frambesia).

Lesions of yaws can be cured with smaller doses of salvarsan.

Serum reaction does not appear as promptly.

Syphilitic rabbits treated with salvarsan can be infected with yaws fourteen days after treatment, while reinfections with syphilis do not occur under the same circumstances.

Advances in immunity and immunity reactions have been of some help in maintaining the dual character of these diseases. Patients with syphilis can be inoculated with frambesia, and respond with the lesions of yaws. Patients with yaws may be inoculated with syphilis and pass through typical primary

and secondary syphilis. Frambesia is autoinoculable, and heteroinoculable even in the secondary generalized stage of the disease. Once the syphilitic spirochete had advanced beyond the local site of inoculation, neither auto-inoculation nor heteroinoculation will succeed.

Serologic diagnosis proved no aid in the subject, or both diseases excite a reaction in the blood of the patient that gives the Wassermann positive result. Castellani at one time believed that the antigen bodies in both diseases were different, but the later discoveries of the nonspecificity of antigen in the Wassermann test have made negative any distinction.

That frambesia tropica is not transmitted from the infected parents, no matter in what period of the disease they may be, to the offspring during the intrauterine existence of the fetus is a strong argument in favor of nonidenity. Hereditary syphilities do not acquire syphilis, yet the writer has seen a case of generalized frambesia in a typical hereditary syphilitic boy who had the Hutchinson triad, notched spade upper incisors, marked iritis, and deafness.

The mother of an hereditary syphilitic child does not acquire syphilis from her offspring, but it is a common observation that an infant with yaws infects its mother. The location of the primary yaw on the nipple and over the ilium where the native mother carries her baby is evidence of this.

Goodman had the opportunity of studying yaws in Porto Rico and Panama. As it exists in those places, it corresponds to the descriptions given under various other names in other parts of the tropics and subtropics. He demonstrated the *Spirochete pertenuis* and corroborates the finding that this organism is morphologically indistinguishable from *S. pallida*. The serology was investigated and five cases gave positive Wassermann tests. Five cases of frambesia were diagnosed among upward of 900 prostitutes. Treatment with arsenobenzol (Schamberg) and novarsenobillon gave beneficial results.

**"Spirochetes" Derived from Red Blood Corpuscles.**—Frederick Eberson, St. Louis. *Archives of Dermatology and Syphilology*, 1920, vol. xxxviii, p. 638.

The simple experiments that have been described, need no exhaustive comment. It is obvious that the search for typical *Spirochete pallida* may be made less difficult if light be thrown on confusing artifacts which, as in this instance, have been interpreted by some in an entirely erroneous manner. It has been shown that spirochete-like bodies are derived from red blood corpuscles. These bodies bear no relationship whatever to the organism of syphilis and may be produced at will. Influences, such as H-ion content of solutions, tonicity and transfer from the usual environment are sufficient for the demonstration of the phenomenon. These nonspecific and inanimate bodies may be seen in specimens of fluid that are apparently free from blood. However, a very careful search of numerous fields will reveal the presence of at least one red blood cell which is all that is necessary for the transformation process. The failure to find red cells in a specimen of testicular fluid is not invalidating proof of the contention that the "spirochetes" are thus derived. Both normal as well as spirochete-infected testicles show these bod-



ies, but their presence has nothing whatever to do with the life-cycle of the specific agent in syphilis. They are merely derivatives of red blood corpuscles.

**A Method for Demonstrating Spirochaeta Pallida in Regional Lymph Glands.**

—Edwin W. Schultz, Stanford University, Calif. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 176.

A 2 or 5 c.c. hypodermic syringe with a sharp needle is employed. Into the syringe is drawn from 0.5 to 1 c.c. of sterile physiologic sodium chlorid solution. The gland is firmly fixed between the two forefingers and thumb of the left hand, and with the syringe in the right hand the needle is passed through the overlying skin and then gently through the capsule of the gland. The point of the needle is then rotated in order to break down some of the gland tissue. After this has been done, the saline solution is slowly injected into the gland, and the capsule swell under the fingers is noted, after which the point is rotated a few times more. Suction is then made with the plunger of the syringe and as much gland-pulp mixture is withdrawn as is possible; but a few drops are generally quite sufficient. Several slides are prepared for dark field examination, special care being taken to select thin slides and cover-slips and prepare the specimens in films of practically capillary thickness. The sort of dark-field technic is all important. In general, the entire procedure of procuring the specimen should be aseptic and carefully done. The modification has proved especially valuable in establishing an early diagnosis in certain cases, and has been employed without any noticeable ill effects on the patients.

**The Blood Wassermann Reaction; Its Theoretic Value, Its Practical Value and Its Failures.**—Nicolas and Gaté (Paris). *Annales de dermatologie et de syphiligraphie*, 1920, June, vi series, i, 3.

This exhaustive article is summed up by its authors as follows: A negative reaction does not exclude syphilis and should not prevent a most thorough clinical examination and treatment test in all doubtful cases. A positive reaction which is antagonized by clinical evidence should always be repeated in a few days. This view, put forth by the writers in 1914 has now been accepted by a large number of authors. It often happens that the second test is negative, which should exclude syphilis. If, however, it is again positive, the clinic and not serology must decide. In such a case the reaction does not call for a treatment test. In treatment we should pay no heed to the reaction but submit the patient to systematic and prolonged treatment with occasional intermissions along the lines laid down years ago by Fournier. In forensic practice a high place should not be accorded to the reaction, and its use in connection with questions of marriage, procreation and life insurance should be much restricted. The laboratory resources should never be underrated but it is possible to overrate them. In the case of the treponema the evidence is flawless but in complement-deviation tests many bizarre cases have come to light. The Wassermann reaction is not strictly speaking a specific one for

syphilis. For example, it has been positive in cases which clinically must have been tuberculides and the authors give a case of mycosis fungoides in which the positive Wassermann led to a diagnosis of syphilis and mention that lichen planus and scabies cases have also given positive results, although neglecting to state whether strongly positive.

**The Interpretation of Reports on the Wassermann Reaction.**—J. H. Litterer, Nashville, Tenn. *Journal of the Tennessee State Medical Association*, 1920, vol. xii, p. 364.

If the clinician wishes to get the most that is possible from a Wassermann report, he must meet the following requirements: (1) He must have a general knowledge of the principles of the test and its sources of error. (2) He should familiarize himself with the general meaning the antigens convey. (3) He must share the history in suspected and borderline cases with the serologist. (4) He must know the effect of antisyphilitic treatment upon the test, and become familiar with those diseases which tend to give positive reactions. He must accept a report as a finding which shall be weighed and taken in connection with other evidence at hand.

**The Practical Value and Utilization of the Wassermann Test in General Practice.**—Robert A. Kilduffe, Chester, Pa. *Archives of Diagnosis*, 1920, vol. xii, p. 125.

A positive reaction may be obtained within eight to ten days after the appearance of the initial lesion, though the results are more constant after an interval of three to six weeks. In untreated, secondary lues, and in tertiary lues, the test is highly specific and of incalculable value. A single negative reaction does not by any means exclude syphilis. Where ground for suspicion exists, the test should be repeated, preferable after a provocative course of treatment. In cases of syphilis of the nervous system the spinal fluid should be examined, as the blood may give a negative reaction. While a positive reaction indicates syphilitic infection, it does not necessarily mean that the lesion from which the patient suffers is syphilitic. A tuberculous or malignant condition must not be overlooked as such because the Wassermann is positive. In obscure conditions a Wassermann should always be made, regardless of the history. Where abortions are frequent, a Wassermann may lead to efficient treatment and the saving of the child. The effects of treatment can and should be followed and controlled by repeated Wassermans. With special modifications of technic, the amount of syphilitic antibody present may be measured with marked accuracy. A single negative does not mean a permanent cure. It is safer to insist upon tests at intervals of three months for a year after treatment has been discontinued. The Wassermann is the most constant single symptom of syphilis and should be resorted to in all cases where the diagnosis is not clear and evident. To secure the maximum results, choose a competent and accessible serologist and treat him as a consultant—

the results will be highly satisfactory and of incalculable benefit in the diagnosis and treatment of a surprisingly large number of cases in every-day practice.

**The Colloidal Gold and Other Cerebrospinal Fluid Reactions.**—Charles E. Nixon, Minneapolis, Minn. *Minnesota Medicine*, 1920, vol. iii, p. 186.

The colloidal gold is the most delicate of the routine spinal fluid reactions. It does not replace any other test but, on the other hand, is of independent value. It is of special importance in the early diagnosis of neurosyphilis. The various curves are not specific but are of great diagnostic value in conjunction with other clinical and laboratory findings. A colloidal gold curve may be obtained with or without other positive findings after provocative treatment. The colloidal gold curve does not parallel clinical signs or give definite evidence of improvement under treatment. Cases with no involvement of the central nervous system give no colloidal gold curve. Clear cut clinical cases of *tabes dorsalis* may show all the spinal fluid reactions negative both before and after treatment. A curve in Zone III with a negative cell count and negative or faintly positive globulin is strongly suggestive of a brain or cord tumor or myelitis. Curves in Zone I and II may be found in nonluetic conditions such as multiple sclerosis and brain abscess. A cell count above 5 is pathologic but this count is of no value in indicating duration or severity of the process or improvement.

**Colloidal Gold Reaction.**—Margaret Warwick, Minneapolis, Minn. *Minnesota Medicine*, 1920, vol. iii, p. 188.

A positive reaction if present at all begins to appear at once and then intensifies for several hours, being complete at 8 or 12 hours. As Solomon and Welles have mentioned, all syphilitic curves appear the same at first, with a paretic one developing later, and are only complete after 12 hours, so that if read too early, a paretic curve may be confused with a syphilitic one. On the other hand, a test showing no beginning color changes at the end of half an hour may as well be discarded as none will appear later. For our readings, we designate an unchanged fluid as 0; a bluish red as 1; a reddish blue as 2; a deep blue as 3; a grey blue as 4; and colorless as 5. Because of the peculiar shades of red, all readings must be done with direct daylight, holding the tubes up against the sky, instead of against green grass or colored buildings. The so-called typical paretic curve shows the first few tubes completely precipitated, giving a colorless solution, while lesser changes may appear in the remaining ones, as 5, 5, 5, 5, 4, 3, 1, 0, 0, 0. The syphilitic curve shows the first one or two tubes unchanged with a maximum color change which is usually 3, seldom beyond 4, in the 4th or 5th tube, as 00 2 3 3 1 1 0 0 0. This includes the curves of both *tabes* and cerebrospinal syphilis as this reaction does not differentiate between them. The so-called meningitic curve which does not distinguish between different types of meningitis or myelitis is designated by the



early writers as "Verschiebung nach Oben" and consists of a curve showing color change in the right half of the tubes with a maximum reaction in the 7th or 8th as 0000013310.

**The Wassermann as a Diagnostic Measure in Primary Syphilis.**—W. H. Guy, Pittsburgh. *Pennsylvania Medical Journal*, 1920, vol. xxiii, p. 341.

The incubation period varied from one day to two months, the very short incubation periods being accounted for by double infections. Obviously then the one to three or four day incubation periods represented the incubation period of chaneroid, but did not preclude the early recognition of syphilis. At the time of finding the spirochete, lesions had been present for periods of time varying from twenty-four hours to eighty days. Repeated examinations were necessary in many cases before the organism was found and in several instances aspiration of inguinal glands revealed the spirochete after direct examinations had proved negative. Practically the original Wassermann technique was used, except that a cholesterinized alcoholic extract of beef heart was the antigen. Degree of reaction was reported as negative, plus-minus, one-plus and two-plus. Location of the lesion, either genital or otherwise, did not seem to determine in any way the date of positive reactions. The earliest positive (one-plus) Wassermann was obtained two days after the appearance of the lesion, in a case with an incubation period of thirty days. Under one week positive reactions were extremely rare. Infections seven to ten days old gave positive reactions in about 10 per cent of cases, the percentage gradually increasing according to the age of the infection up to forty days when 98 per cent of reactions were positive. Only two cases with lesions more than forty days old gave negative Wassermann reactions. Therefore, the author insists that early, careful repeated dark-field examinations are of vital importance, and that negative Wassermann reactions early in the course of venereal ulcers are not to be accepted as evidence of the absence of syphilis.

**Further Observations on Neurosyphilis and the Psychoses.**—Lawson G. Lowrey, Boston. *Archives of Neurology and Psychiatry*, 1920, vol. iii, p. 500.

Nineteen cases are presented, of which fourteen are undoubted cases of neurosyphilis, one a case of pseudoparesis and four have negative physical and equivocal serologic findings. Of the fourteen undoubted cases, only four present clinical evidence from which a diagnosis of neurosyphilis could be made. Neurosyphilis occurs more frequently in association with paranoid psychoses than is usually recognized. Although six cases are here reported, not one is a clear example of the syphilitic paranoid psychosis, two being heavily alcoholic, one a paretic, and two possibly not neurosyphilitic, though showing changes in the spinal fluid. Any type of abnormal mental state, or no abnormal state, may occur with neurosyphilis. It does not follow that all such cases are paretic. Serologic findings may definitely increase under treatment, with or without increase of clinical signs, emphasizing the importance of provocative treatment in rare cases. A negative blood Wassermann reaction, or many

such, are not always conclusive negation of the presence of neurosyphilis. A negative spinal fluid is not absolutely conclusive evidence of the absence of neurosyphilis. Since neurosyphilis may exist in association with any type of mental symptoms, and since such states may exist in the absence of any of the usual signs and symptoms of neurosyphilis, it follows that lumbar puncture should be done at least in all cases which present any atypical features. It is equally important to puncture cases with any clinical signs of neurosyphilis, since the signs may be misleading. The prognosis and treatment of any cases are always modified by the presence of neurosyphilis. Neurosyphilis as a disease may exist for a long period before symptoms appear.

**Anticipation of Paresis and Tabes in Syphilitics.**—Sanger Brown, Kenilworth, Illinois. *American Journal of Insanity*, 1920, vol. lxxvi, p. 397.

With a view of accumulating the desired histories the author ventures to offer the following suggestions: 1. A committee embracing representatives of the various branches of medical science should be formed to elaborate and submit or perhaps execute plans for the achievement of the end in view. Among the subjects which should engage the activities of such a committee might be mentioned: 2. Securing sufficient financial support; for without the assurance of this it would be idle to proceed. A bureau would have to be established from the first to carry on correspondence and disseminate literature essential to successful prosecution of the several features of such plans as might be adopted. This would involve the permanent employment of a qualified executive with appropriate quarters and assistants. 3. Preparation for a prospectus and propaganda to aid in the formation of a league of physicians, whose members would undertake to supply the necessary histories. 4. Devising a scheme for history taking with reference to scope, uniformity and conciseness, and for analysis and classification of histories, and also providing for continuity of observation when the patient might change his residence. 5. And finally contrive measures for securing and maintaining the interest and cooperation of the patient, and convincing him that nothing would be required of him that might in any way compromise his right of privacy.

**The Diagnostic and Prognostic Value of Positive Spinal Fluid Findings in Syphilis.**—P. Goldberger. *Wiener medizinische Wochenschrift*, 1920, No. 30-32, p. 1346.

Upon the basis of his investigation of the diagnostic significance of "positive" findings in the spinal puncture fluid of syphilitics, the author arrives at the following conclusions: In order to guard against all undesirable sequelæ of salvarsan, in the form of neurorecurrences, all syphilitic patients should be subjected to control examinations of the puncture fluid, beginning at about the tenth month of the infection. A single control does not suffice, as the meningeal infection may take place at an abnormal time, in view of the variegated course of syphilis. Especially when the first findings were weakly positive, a second control is necessary for the decision between meningeal in-

fection and abnormal spinal fluid. The control of the fluid is most advantageously carried out simultaneously with the withdrawal of blood for the Wassermann reaction. A meningeal infection which has run its course in the early stage of syphilis cannot be utilized for prognostic conclusions of any kind. A single demonstration of a reaction in traces, during the remote latent stage is not sufficient to justify a favorable prognosis. The findings must be made at different intervals of time and remain approximately alike; abnormal vascular permeability must be absent. Remote latent cases with completely positive findings must be tested especially as to the vascular permeability of the meninges; its presence presumably aggravates the prognosis. In view of the available material of clinical facts, it is desirable to examine the pathogenetic relations between diseases and functional anomalies of the cardiovascular system on the one hand, and the hereditary nervous affections on the other; functional tests of the cerebral vascular system through introduction of pharmaceutical agents would seem to be promising in this respect. In many cases, a reliable estimate of the spinal fluid can only be rendered in conjunction with all the other clinical findings.

**Syphilis at a Venereal Clinic.**—E. F. Skinner, Sheffield. *Lancet*, London, 1920, vol. cxcviii, p. 650.

Primary cases are still in a grave minority of admissions. Women do not seek advice in the primary stage, and steps should be taken to disseminate knowledge of the dangers of venereal disease and the advantages of the clinics amongst the female population. Continuity of treatment is essential for cure, and discontinuity a possible danger. Only where treatment is commenced before the Wassermann reaction has become positive can a cure be definitely promised.

**The Prognosis in Syphilis.**—Morfini *Revue Médicale de la Suisse Romande*, 1920, vol. xl, No. 9, p. 541.

The importance of spinal puncture in syphilitic patients is emphasized by the author on the basis of a personal observation of specific meningitis in a man forty years of age in whom the Wassermann reaction was already positive at the end of thirty-five days after the date of the infection. Spinal puncture in the course of the specific infection permits the determination of two periods during which the meningoencephalic or medullary lesions are especially pronounced. Very early in the disease, the central nervous system is violently invaded, corresponding to the last days of the period clinically considered as primary, and most distinctly manifested at the onset of the eruptive stage, clinically known as secondary lues. Later on, during a variable length of time which still belongs to the secondary stage and in the course of which the luetic infection manifests itself in the form of buccopharyngeal mucous patches, genital erosions, large condylomata, etc., the disturbances of the nerve centers, revealed by the examination of the cerebrospinal fluid, seem to diminish in severity, at any rate in a large number of the cases. Next follows a time



when spinal puncture again reveals more pronounced nervous lesions, in the clinical tertiary period. Patients suffering from sclerogummatous or ulcero-tubercular lesions of the tertiary type often present a considerable hyperlymphocytosis. This remark applies to untreated, irregularly or incorrectly treated cases, for these clinical lesions of the tertiary type are very exceptional in syphilitics who have been subjected to energetic treatment. In patients having typical clinically demonstrable nervous lesions, it is not surprising that the spinal puncture findings confirm the results of examination of the body. The explanation of the facts outlined above is probably as follows: At first, at the time when the syphilitic infection becomes generalized, in the preeruptive period and beginning of the eruptive period, the patient has not yet been able to mobilize his defensive mechanisms. He possesses only a weak immunity towards the microbic invaders; as illustrated by the numerous cases in which the Wassermann reaction is still negative three to four weeks after the appearance of the chancre. As a rule it does not become positive until the appearance of the rash, or the days immediately preceding the skin eruption. From this time on, the patient possesses antibodies; he fights, tending to localize his lesions, and is no longer in a state of actual septicemia. Thus it is hardly surprising that the usually strong reactions of his nervous system at the time of generalization of the luetic infection will now begin to improve. Still another factor intervenes and modifies the picture: the patients are under treatment, and the author was enabled to demonstrate in a large number of cases, by means of spinal puncture repeated two or three times in the same patient, in the course of six to eight weeks, that the inflammatory phenomena at the level of the neuraxon evidently diminished parallel with the subsidence of the clinical manifestations of the disease. Tertiary syphilitics in whom the condition of the cerebrospinal fluid indicates an inflammatory process in the nervous system, are practically all untreated or very insufficiently treated cases. There seems to be no doubt about this observation. Specific treatment, energetically applied, acts favorably upon the development of the lesions of the neuraxon, revealed by examination of the cerebrospinal fluid. This fact could be very frequently demonstrated by means of repeated spinal punctures in the same patient in the course of treatment.

The case observed by the author furnished proof that in spite of energetic treatment, in the absence of all clinical or subjective symptoms pointing to involvement of the central nervous system, the latter is no less threatened with a very early and serious invasion. This man felt very well, the Wassermann reaction of the blood was negative, and he had never suffered from nervous disturbances. Having been subjected to energetic treatment, he was apparently protected against all unwelcome surprises. But less than eighteen months after the onset of the disease, five weeks after the last injection of 606, he was suddenly overwhelmed by meningoencephalic symptoms which could undoubtedly have been foreseen and avoided through the application of a spinal puncture at the time when the last (negative) Wassermann reaction was taken. It is not possible to determine definitely by means of the ordinary methods of examination and control, whether or not a luetic infection takes a

favorable course. Spinal puncture is a method of examination which cannot be dispensed with by conscientious clinicians. It should be kept in mind that in old cases of syphilis, especially of the nervous system, the Wassermann reaction may be negative in the blood while it is positive in the cerebrospinal fluid. No prognosis can be rendered without spinal puncture, and treatment of the luetic infection is therefore apt to be deficient and insufficient.

**Mortality and Morbidity of Infected and Noninfected Offspring of Syphilitics.**

—M. Kaufmann-Wolf and E. Abrahamsohn. *Zeitschrift für Klinische Medizin*, 1920, lxxxix, p. 274.

The author investigated the mortality and morbidity of infected and non-infected offspring of syphilitic parents, and on the basis of their findings in five series of cases arrived at the conclusion that children of syphilitics undoubtedly constitute an extremely diversified material as regards the damage sustained by them through the luetic disease of one or both parents. Theoretically speaking, present experience indicated that all children may escape when the parent at the time of procreation was in a late state of noninfectious syphilis, whereas on the other hand, the most desperate pictures of congenital syphilis may be noted in all children without exception when the marriage was consummated in the highly infectious primary or secondary state. In determining the mortality, or morbidity, respectively, of syphilitic progeny, it is necessary in the first place to take into consideration the date of the parents' infection, and to ascertain whether or not an infection of the mother has occurred. In marriages from which children with parenchymatous keratitis were born, a mortality of 53 per cent was noted. In marriages where one of the children suffered from juvenile tabes, the mortality amounted to 64 per cent. The mortality of the offspring of paralytics probably attains at least 70 per cent, especially in case of maternal infection. In a general way, without any attempt at differentiation, the mortality of the offspring of syphilitics would seem to average about 50 per cent. The morbidity of the children, without differentiation, amounted to 50 per cent. Accordingly under the most favorable conditions, at most one quarter of the progeny on an average seem to be healthy. (These observations were made in the Berlin University Polyclinic for Cutaneous and Venereal Diseases.)

**The Need of Hospital Beds for Syphilis.**—John H. Stokes, Rochester, Minn. *Modern Hospital*, 1919, vol. xii, p. 1.

Syphilis is often recognized by the hospital serologist when no other signs present themselves. The hospital serologist, by reason of training and environment, is specially fitted to be the performer of an authentic and trustworthy Wassermann, which is badly needed in these days. Of 500 patients examined by Horner (Boston City Hospital), 16 per cent had syphilis, although only 2 per cent had been identified by other means than the Wassermann. Syphilis needs, for the proper care of its medical, surgical, neurological and special complications, the prolonged observation, cooperative diagnosis, and

control which only a stable, well-organized hospital service can supply. The actual technic of the intensive treatment of syphilis requires beds. Therapeutic control, a low mortality, and the successful management of the very sick patient, which is much commoner in syphilis than is generally recognized, all demand something more than ambulatory facilities. The hospital bed service is needed for a brief but necessary quarantine, which can be carried out without the slightest risk to other patients or the medical and nursing staff. Well-organized treatment for syphilis, such as a hospital service can provide, has the same value in syphilis as sanatorium care has in tuberculosis. It is a factor in inculcating a sense of social responsibility in the patient and in encouraging ideals of rehabilitation and cure. Organized hospital care of syphilis provides centers for the follow-up control so essential in the disease, for the development of the record systems, and for the outside professional cooperation essential to adequate treatment. The hospital service provides the only place in which syphilis can be made a subject of thorough study and research.

**Effect of Mercury Salicylate on the Wassermann Reaction, Observations on the Serology of 87 Previously Untreated Men.**—Herman Goodman, *Archives of Dermatology and Syphilology*, August, 1920, p. 193.

Goodman gave 87 previously untreated syphilitic patients with four-plus Wassermann reactions one grain of mercury salicylate intramuscularly at weekly intervals for courses of from six to eight injections. The Wassermann reaction immediately after treatment remained strongly positive in 66 per cent of the cases. In only nine per cent was there a reversal to negative; and in some such patients who were given a third Wassermann test after an interval without treatment, the reaction was positive. It seems fair to conclude with Anderson and Nelson, who carried on a similar study in 1915, that mercury salicylate alone and for the period given does not qualify as a curative agent in syphilis. The plans for a longer study were curtailed by the demobilization. In the future, mercury salicylate will be used in increasing doses up to 2 and 2½ grains weekly in an effort to learn whether mercury salicylate in larger doses is effective.

**Mercury in the Treatment of Syphilis.**—Louis D. Smith, Chicago. *Illinois Medical Journal*, 1920, vol. xxxvii, p. 308.

In conducting this work it was the author's object solely to determine whether or not it was possible to use the drug safely as an intravenous medication, which method appears to him to be ideal in giving mercury. The dose absorbed is thus measured and the method painless. The question as to whether mercury or salvarsan is the best remedy does not enter here, although the combined treatment is recognized to be proper. He believes that it is here demonstrated that mercuronal in a dosage of 5 c.c. containing over one-half grain mercury answers the question of mercury medication more than



well, since it is possible by its use to employ a larger dosage of mercury more safely and painlessly than any other form. It will be interesting and important when the product, mercurosol, which is not yet on the market, will be given further and extended trials, as it lends itself to easy administration.

**Mercuric Iodide in the Treatment of Syphilis.**—R. L. Spittel, Colombo. *Lancet*, London, 1920, vol. cxcviii, p. 378.

The dose for an adult is 8 to 12 c.c. given intravenously with a 20 c.c. or, better, a 30 c.c. syringe. The required dose is filtered off through aseptic cotton-wool and drawn into the syringe, which is then filled to its full capacity with strained sterile or distilled water. This further dilution, with at least an equal quantity of water, preferably more, is necessary to prevent pain and thickening of the vein; a 30 c.c. syringe is therefore necessary for the larger doses. Should any of the solution escape into the tissues outside the vein a tender induration results as with salvarsan. Unless exceptionally well borne a dose of 12 c.c. need not be exceeded. The injection is tolerated well. Heavy doses may cause chill, fever, malaise, and abdominal pains with diarrhea (sometimes bloody), and griping; but there is scarcely any reaction when an initial dose of 7 or 8 c.c. is given and gradually increased by 1 or 2 c.c. at a time, according to tolerance. Gingivitis and salivation give the clue to quantity. Heart and kidney disease need not stand in the way of careful dosage. The rapidity with which these injections cause the disappearance of syphilitic lesions is indeed gratifying; the results are not only far quicker than those obtained with mercury and iodides given by any other methods, but often even a single injection produces an effect almost as phenomenal as salvarsan. In nerve syphilis especially some of the finest results are obtained; this is not to be wondered at when the absorptive action of iodides is remembered. The number of injections and the interval between them vary, of course, with the particular case. An ordinary case of secondary syphilis may be treated with five or six injections each of salvarsan and mercuric iodide, given at intervals of from seven to ten days alternately, in varying sequence or in successive courses. Often after such a series a negative Wassermann reaction is permanently obtained; if not, further courses are given to meet particular needs.

**Silver Salvarsan.**—F. Bering. *Deutsche medizinische Wochenschrift*, 1920, No. 20, p. 538.

The author's contribution is based on 3,200 infusions of silver salvarsan, in 127 men and 132 women, in the Essen Dermatologic Clinic. It was found that the manifestations subsided very promptly in all stages of syphilis, with rapid disappearance of the spirochetes. In his experience, no venous thrombosis occurred under employment of silver salvarsan. Eruptions and icterus were not more commonly observed after silver salvarsan than after the older salvarsan preparations. Silver salvarsan is well adapted to the abortive

treatment of syphilis. Under combined silver salvarsan and Hg treatment, a very favorable and long-continued influence on the Wassermann reaction was noted in the author's material. The combined treatment seems still to be required at the beginning of the secondary period and is undoubtedly much more efficient, although a favorable influence of silver salvarsan alone is undeniable. According to the author's experience, it might be advisable to prescribe in the first place two courses of combined silver salvarsan and Hg treatment, subsequent treatment to consist of silver salvarsan alone. The first two courses should be administered in rapid succession, being of decisive importance for the welfare of the patient. With special reference to tabes and cerebral syphilis, a definite verdict cannot as yet be rendered, although the tabes was apparently favorably influenced. Very likely reactions on the part of the tabetic phenomena were occasionally noted, for example, pains in the legs. In the treatment of cerebral lues, silver salvarsan is a very suitable preparation, judging from the author's experience. Cutaneous and mucous lesions subside promptly, and late syphilides likewise react favorably. The effect of silver salvarsan is regarded by the author as equivalent to the effect of old salvarsan, with due credit to the smaller dosage and the smaller contents in arsenic of the new preparation. The toxicity of silver salvarsan is not increased under simultaneous administration of mercury.

**Experiences with Silver Salvarsan.**—K. Wiener. *Deutsche medizinische Wochenschrift*, 1920, No. 25, p. 680.

A comparison of the effect of the various salvarsan preparations meets with difficulties, even on the basis of relatively large material. Working in the Breslau University Clinic for Skin Diseases, the author endeavored to obtain the most favorable conditions for such a comparison, by standardizing a large number of silver salvarsan cures in regard to dosage and intervals, of course taking into consideration the patient's individuality and contraindications due to reactionary manifestations. Under employment of his method, he finds that sodium silver salvarsan is not essentially more inconvenient or difficult to handle than neosalvarsan or sodium salvarsan, provided the operator is sufficiently skilled in intravenous injections and the same caution is employed in the preparation of the solution. No spinal apparatus is required. The curative effects in primary lesions, secondary and tertiary symptoms are very favorable, and apparently not inferior to the results of a combined course of neosalvarsan and Hg in the customary dose. The same is true in regard to the Wassermann reaction, but this point remains to be confirmed by essentially longer and more numerous observations. Whether or not dermatoses are more common with silver salvarsan than with the other salvarsan preparations, cannot be decided on the basis of the available material, and the same remark applies to early and late leterus. Judging from the author's experience, thromboses seem to be somewhat more frequent, in spite of absolutely correct intravenous injection. So-called neurorrecurrences have not been ob-

served in the author's clinic for several months past. The statement can be made that treatment with silver salvarsan without Hg in individual doses of 0.05 to 0.25 and in total doses of 2-3 g. has so far yielded entirely successful results in seronegative lues. Also in seropositive lues, an inferiority of this remedy as compared to the customary moderately strong combined treatment could not be observed, aside from occasional and still doubtful neurorecurrences. Silver salvarsan can be recommended for continued trial in suitable cases.

**Accidents Following Intravenous Use of Arsenobenzol.**—Lortat-Jacob, Paris, *Le Progrès Medical*, July 17, 1920, vol. xlviii, 29.

The author writes with especial reference to the so-called "status anterior" and to the factors active in intolerance. The accidents attributable to arsenobenzol have been discussed magistrally by Gastou, and the author wishes only to add a few comments. Numerous vascular accidents are extremely slow in developing and the author isolates certain toxic phenomena which are precocious. He concentrates on a dysthyroidism in which previously no evidence of this condition had appeared save a recurring diarrhea. These crises show the meaning of the term "status anterior." One such patient subsequently developed the full picture of Graves' disease but in this particular case there was no history of syphilis at any time and no salvarsan treatment. The bearing of this case is apparently that the arsenical compound might be able to precipitate phenomena of dysthyroidism and that the crises of diarrhea and other phenomena may serve as a caution. The author knows of dysthyroidian subjects who have reacted in a peculiar manner to arsenicals, sometimes by a febrile reaction, and as a rule there is dissociation between pulse and temperature. He believes that a second injection before this reaction has subsided is contraindicated. This subsidence may require several weeks, for there may persist a slight rapidity or instability of the pulse which is traceable to the first injection. In some of these cases the gland is distinctly enlarged during this cycle. The condition whether as a preexistent state or one activated by an injection should be somewhat amenable to opotherapy to which minute doses of arsenic could be added to lessen the sensitiveness of the subjects to intravenous salvarsan. No cases are cited.

**Mercurial Stomatitis.** G. Maurel. *Gazette des Hôpitaux*, vol. xciii, No. 80, p. 1269.

There exists a type of partial mercurial stomatitis of medicinal origin in which the portion of the gums in contact posteriorly with the last large lower molar, usually the wisdom tooth, is affected. The tooth becomes loose, and behind it appears a small movable floating red rim, constituting a retro-molar detachment of the gums. This lesion may be bilateral, but is very often limited to the right or the left side alone. The condition at this stage



is often overlooked by the physician and not complained of by the patient, as there are only slight functional disturbances in the form of tension and irritation. Another type of mercurial stomatitis is represented by peripheral gingivitis, and manifests itself around a carious tooth, an old root or stump, or a fragment of crown. The medicinal agent here merely increases an inflammatory process, a chronic gingivitis which has created a point of lessened resistance. One of the most common modes of onset of mercurial stomatitis consists of inferior mesial gingivitis, the process originating at the neck of the lower middle incisors, than of the lower lateral incisors. As a rule the vestibular portion of the gums is alone involved, the lingual portion ordinarily remaining intact. The teeth at this level are encircled below by a purplish margin, consisting of the red and swollen gums. Digital pressure on the gums, passing upwards to the neck of the tooth, causes a droplet seropurulent fluid to appear under the detached gingival border. Sometimes, irregular painful and extremely obstinate ulcerations are observed. The patients complain of loose teeth and pain on mastication, besides a metallic taste in the mouth. In certain cases of lateralized or hemistomatitis, the mercury seems to exert its action on only one side of the mouth, while the other remains intact, but this is due to the patient's resting habitually on the right or the left side. In the severe forms of mercurial stomatitis, the loose teeth are covered with a fetid layer reaching to one-third or half of their height, which can be removed without difficulty, like the coating of the tongue.

**Treatment of Syphilis with Silver Salvarsan.**—Dargallo, Madrid. *Revista Española de Medicina y Cirugía*, March, 1920, vol. iii, No. 3.

This article appears to be a synthetic review of the experience of others, almost entirely Germans, whose papers appeared originally in the *Münchener medizinische Wochenschrift*, *Deutsche medizinische Wochenschrift*, and other German periodicals. The dates of the articles are all recent, none earlier than 1919, and the leading authors are Kolle, Hahn, Dreyfuss, Hoffmann, von Notthaft, Galewsky, Stern, Fabry, Levy-Lenz, Voigt, Friedlander, Nolten, Riecke, Nageli. Several of the preceding have published more than one article. As this literature has doubtless been inaccessible to the American reader a digest of the finds should be of interest, but the editor does not attempt any consensus of sentiment and there are numerous minor differences in indications and technic. Galewsky alone has made over 2,000 injections and reports good results especially in tertiary lesions of the skin, aorta and even in early tabes. Hahn praises the remedy especially in early syphilis. Kolle would use the remedy alone while Hoffman combines it with mercurials. Of much interest are accidents and untoward phenomena referable to treatment. There appear to be an extraordinary number and variety of these although not necessarily a high percentage as many thousands of injections must have been made by the dozen reporters. Among the results of this type may be mentioned in succession several fatalities, anaphylaxis, edemas especially of the eyelids, spirochetic fever, so-called, various dermatoses, icterus, headache,

etc. After 12 injections the seroreaction becomes negative even in most of the chronic cases while one or two injections are sufficient to banish the spirochetes. In resumé Galewsky likes the remedy because it is efficacious in very small doses, Hahn because of the rapid action. Dreyfuss who is a neurologist, writes largely of the untoward effects in nervous subjects.

**Treatment of Syphilis by Subcutaneous Injections of Sulpharsenol.**—Emery and Morin, Paris. *Le Bulletin Medical*, June 16, 1920, vol. xxxiv, No. 31.

The authors cite the original drawbacks of the subcutaneous method of exhibiting arsenobenzol, which led to the choice of the intramuscular route. Numerous attempts were made to improve the technic, but these were all in vain. The intramuscular route was in turn supplanted by the intravenous, and both patients and practitioners welcomed the freedom from local accidents by the latest method. This in turn showed certain disadvantages and once more there was a search for hypodermic method with a minimum of disadvantages. It was found that novarsenobenzol gave some encouragement in this direction but there was a great deal of room for improvement. At this juncture Levy-Bing and others experimented with sulpharsenol which it was claimed exhibited an unusual degree of local tolerance. It does not appear that any of the men in question used the method by the subcutaneous route, the intramuscular being the one invariably mentioned by the reporters. The present authors began with intramuscular injections and found that while the local reaction was an improvement over that which follows exhibition of the older arsenicals there was a possibility that the subcutaneous route would prove an advantage. This step was the more welcome because with the new substance general reactive phenomena had been absent. The result was all that had been expected and the authors announce that the net sum of the advantages minus the drawbacks is in favor of the subcutaneous route. The therapeutic results were apparently not inferior in any respect and the absence of general and minimization of local reactions conspicuous. However, the authors for the present justify the subcutaneous route only when the practitioner is inexperienced and in the case of an experienced man only when the veins are difficult of access, and of course when previous attempts at intravenous or intramuscular exhibition have been prejudicial.

**Report on Fifty-eight Cases of Delayed Arsenical Poisoning, Following the Administration of "606" Preparations.**—George S. Strathy, C. H. V. Smith, and Beverley Hannah. *Canadian Medical Association Journal*, 1920, vol. x, p. 336.

Fifty-eight cases of delayed poisoning following administration of "606" and mercury were observed. Forty-seven of these showed symptoms referable to the liver; namely, jaundice, decreased digestive power and liver atrophy. Eight of these were fatal and at autopsy showed marked atrophy of the liver. Atrophy of the liver may be marked in cases which ultimately

recover. This condition can be diagnosed by x-rays. Dermatitis occurred in eight cases. Five were severe with marked exfoliation. Peripheral neuritis was observed in two cases. Albuminuria was present in over 50 per cent of the cases. Edema was found in two cases. The onset of the symptoms seldom occurred until five weeks after the administration of "606" had ceased. The earliest symptoms of "606" poisoning of the liver were, bile in the urine, albuminuria, loss of appetite and jaundice. These symptoms should be looked for in all patients receiving "606" treatment, and on their appearance the administration of "606" should cease. By x-ray examination, atrophy of the liver may be diagnosed at an early stage. Where evidence of liver damage is present, the diet should be reduced to a minimum. Dermatitis with atrophy of the liver occurred in one patient who received arsenic in the form of Fowler's solution, minims v., t. i. d., for five months. The authors believe these were cases of delayed arsenical poisoning.

**Toxic Jaundice in Patients under Antisyphilitic Treatment.**—Cameron V. Bailey and Angus MacKay, Woodstock, Ontario, Canada. *Archives of Internal Medicine*, 1920, vol. xxv, p. 628.

In patients whose livers are damaged by arsenobenzol derivatives, an increase of cholesterol in the blood is an early and marked sign; it persists after other clinical signs have disappeared; its routine estimation may be of value in detecting the onset of liver injury in patients under antisyphilitic treatment. In debilitated patients, the oxidative activity of the urine is decreased. This decrease is much more marked if the liver is disordered. In such cases the oxidative activity is greater during absolute rest. Exercise should be restricted greatly during the course of antisyphilitic treatment and for the following few weeks. A diet, rich in carbohydrate and very low in fat and protein, should precede, accompany and succeed the administration of arsenobenzol derivatives in the treatment of syphilis. Increase of protein in the diet, and of exercise, should be controlled by the estimation of the urea in the blood. The appearance of toxic symptoms in delayed poisoning by arsenic, phosphorus, chloroform, etc., is possibly due to the premature increase of protein in the diet, and of exercise in these cases.

**Can Arsphenamine Be Kept in a Permanent Solution?**—Otto Lowy, Newark, N. J. *Journal of the Medical Society of New Jersey*, 1920, vol. xvii, p. 167.

Solutions of arsphenamine as prepared by the author have remained apparently unchanged for five months and passed toxicity tests of his own and two other laboratories. Clinical tests have shown that it is nontoxic and apparently does not give more reaction than those that occur with freshly prepared solutions. The advantages of this form of arsphenamine require little explanation. The average physician has neither the facilities nor the time to prepare arsphenamine. Further experiments are being conducted in collaboration with the Hygienic Laboratory to determine the rate of deteriora-



tion, if any. Since writing this report over 2,000 injections have been given at various clinics with comparatively few reactions. The solution has also received the approval of the United States Public Health Service and of the Council on Pharmacy and Chemistry of the American Medical Association.

**Further Observations on the Presence of Arsenic in the Spinal Fluid.**—George W. Hall, Russell J. Callender and Edward C. Holmblad, Chicago. *Archives of Neurology and Psychiatry*, 1920, vol. iii, p. 631.

Arsphenamine given intravenously in 0.6 gm. doses may be detected in the spinal fluid in from 25 per cent to 35 per cent of the cases. Irritation of the meninges by the injection of autoserum into the spinal canal does not increase the percentage.

**Post-Salvarsan Jaundice.**—Rupert Hallam, Sheffield. *Lancet*, London, 1920, vol. excviii, p. 1356.

A considerable number of patients suffer from jaundice following the injection of 606. It occurs relatively more frequently after the 914 group of arsenobenzol preparations (neosalvarsan, neokharsivan, novarsenobillon, etc.). It may occur in epidemic form. The causation is as yet undetermined.

**A Preliminary Report on the Use of a New Arsenical Compound in the Treatment of Syphilis: "Mon-Arsone."**—B. L. Wright, U. S. N., L. A. Kennell, U. S. N. and L. M. Hussey. *Medical Record*, 1920, vol. xevii, p. 607.

From their investigations the authors believe they have demonstrated that the standard laid down for an ideal arsenical compound in the beginning of this paper has been fulfilled in mon-arsone. It is decidedly less toxic than the arsphenamine compounds as evidenced by the fact that 0.6 of a gram of arsphenamine, containing 186 milligrams of arsenic (2.8 grains), the maximum dose of this drug, frequently produces distressing and sometimes fatal reactions, while mon-arsone, in 2.4 gram doses, containing 1.064 gram arsenic (16.7 grains) has failed to produce a reaction or a toxic symptom of any description. Mon-arsone is perfectly soluble in small amounts of hot or cold water and may be administered in solutions in which each c.c. represents 200 milligrams of the dissolved solid without the slightest danger. Its singular property of having no hemolytic action upon the red blood corpuscles in this heavy concentration makes such a concentration unobjectionable. It requires no special apparatus for its administration. It contains approximately seven per cent more arsenic than arsphenamine. The solutions of mon-arsone are so stable that they completely resist oxidation or decomposition when boiled or subjected to the higher temperatures and pressures of the autoclave. While mon-arsone is designed to be administered intravenously, accidental extravasation from the vein need not be feared, for from our premeditated subcutaneous injections of this drug and from several accidental leakages from out the vein no untoward results have been noticed. These

manifest advantages make it possible for any well qualified physician to administer this treatment as a routine office or bedside procedure, and render it possible for the naval and army surgeon to have this desired therapeutic agent at his command at all times whether at sea or in the field. Mon-arsone has passed all the requirements demanded for arsenicals by the Public Health Service, having successfully met the established tests prescribed, and made in the Hygienic Laboratory, Washington, D. C.

**Treatment of Tuberculous Syphilitics.**—Verdes Montenegro Madrid. Abstract from *Los Progresos de la Clinica in Revista Medica Cubana*, January, 1920, vol. xxxi, i.

The author discusses the subject at great length, isolating several clinical groups of mixed cases and laying down the management for each, but in the absence of case histories and statistics and of any summary the article does not lend itself to an abstract. In recent tuberculous lesions in a subject of tertiary syphilis he does not see the necessity of suspending the iodides. In more or less advanced cases of pulmonary tuberculosis in old syphilitics the rule should be to treat the disease which is most in the ascendance. Only in marked cases of pulmonary involvement would he refrain from using salvarsan. He finds that fibroid phthisis in youth is responsible for very many cases of chronic bronchitis and emphysema in later life to say nothing of arteriorenal disease; hence when these subjects contract syphilis iodides are perhaps doubly indicated. The author speaks of a case of specific aortitis associated with progressive pulmonary phthisis in which after a short course of mercurials he switched to iodides and relieved the symptoms due to vascular lesions without prejudice to the tuberculous component the latter affection pursuing its customary course. Drawbacks from the use of salvarsan may be compared with those of tuberculin injections. The former should be avoided as a rule if high fever is present while it may be used without fear in fibroid cases. The author holds that syphilis does not unfavorably influence the course of tuberculosis.

**Treatment of Syphilitic Aortitis.**—Vanquer. Laubry and Donzelot (Paris). *La Presse Médicale*, May 29, 1920, vol. xxviii, 35.

Treatment of syphilitic aortitis must be rapid and energetic and should comprise an arsenomercurial cure of 7 or 8 injections of novarsenobenzol 8 days apart with dose beginning at 10 cgm. and increased if necessary to 45 cgm. During the 8 day interval there should be an intravenous injection of mercury cyanate, 1 or 2 cgm. every 2 days. Second, there should be an iodine cure, an oily preparation being injected intramuscularly: this should be repeated every 3 or 4 months at first and eventually with a longer interim. Indications and contraindications should be based on the general resistance of the patient, the state of the kidneys and state of the myocardium. There are two clinical types of aortitis, in one of which there is cardiac insufficiency while in the other the compensation is good. In the latter case the arsenomercurial

treatment should suffice while in the former it may be necessary to abstain from arsenic and mercury and to depend solely on iodine combined with cardiotonics.

**Critique of the Present Antisyphilitic Treatment.**—Calico, Madrid. *Revista Espanola de Medicina y Cirugia*, May, 1920, vol. iii, 23.

The author quotes the dictum of Professor Peyri that from one to six years make up the doubtful period in which we cannot say that a given subject is or is not cured. But if in addition we have visceral syphilis or parasymphilis no limit of any length can be set up unless a permanent negative Wassermann is attainable. Umbert, another authority, has recently stated that the question of cure or no cure is conditioned by at least seven factors, viz: elapsed time; interval between infection and first treatment; nature of the treatment referred to; the sum of all the manifestations of the disease since the first appearance of the chancre; the last manifestation; the state of the patient's health at the time and the serological finds. The two opinions coincide in substance. The calculus of probabilities may be used in the consideration of the seven factors of Umbert to decide on the prognosis in a given case. The author lays much stress on the dangers of mercurials which are in some sense parallel with those of salvarsan. Thus mercury seems able to cause in rare cases a hemorrhagic encephalitis (case of Ptotzl and Schuller). The mercury-resistant subject is seen now and then, and it is possible to saturate him with the metal without in the least benefiting the disease, so that a special cachexia results. Despite our alleged specific treatment the number of deaths due annually to syphilis has been placed at 60,000 for Germany and about half that number for France. These 90,000 comprise a huge infant mortality including stillbirths, together with visceral and nervous syphilis and the rôle played by syphilis in deaths with other diseases such as tuberculosis. These deaths occur despite mercury and, the author intimates, often because of it. The arsenicals have caused many deaths since their introduction and the author appears to believe that we should look elsewhere for remedies.

**Nervous Syphilis and Its Treatment.**—F. Levy, Paris. *Gazette des Hôpitaux*, July 24, 1920, vol. xciii, 65.

The author refers first to the new dualistic hypothesis which is founded on the following evidence. First, cases of metasymphilis have been traced to the same lax women; second, aboriginals who may have the severest cutaneous syphilis never show metasymphilis; third, metasymphilis commonly occurs after abortive attacks of syphilis; fourth—according to some authors only—metasymphilis may occur even in the earliest and best treated cases; fifth, metasymphilitics may contract dermosymphilis anew and are not protected against it. To all the preceding it may be added that experiment has been made to sustain the dualistic hypothesis. Sicard and others have answered all of these contentions, and generally speaking they can be refuted up to a cer-



tain point. Fallacies are involved, for they take no account of the special soil of the patient. As matters now stand it is possible to make a sound argument for either side while no overwhelming or crucial arguments can be adduced. Nervous syphilis may be arterial or parenchymatous according as the treponeme settles in the vascular walls or passes through them to gain the parenchyma. For metasyphilis to develop the latter must have been attacked while the vessels may or may not show lesions. In the diffuse vascular form the meninges may be involved. This conception is complicated and sometimes conflicting. Late lesions imply the existence of earlier ones involving the same areas. Meningitis of the secondary period may be latent clinically. Passing by the subject of diagnosis the author says under treatment that we "must always try." As long as there are arterial lesions only, there is hope of cure and, in mixed cases perhaps, of improvement. Lesions of the meninges alone are also amenable. Resistant of treatment are only the parenchyma, and, as in tabes, the sclerosing process in the glia which may possibly be able to respond somewhat to treatment.

**Neurosyphilis Prophylaxis.**—G. H. Hampshire, Marlin, Texas. *Texas State Journal of Medicine*, 1920, vol. xv, p. 365.

Early spinal puncture will often enable the wary physician to institute measures that will prevent paresis, optic atrophy and tabes. It enables the physician to have a more definite idea as to what his treatment is doing for his patient, no matter what that treatment may be. As infection of the nervous system comes during the secondary stage, delay beyond this period in doing lumbar puncture for diagnostic purposes means the loss of invaluable time if we expect to reduce the number of tabetics, paretics, etc., by early intensive treatment. As investigation indicates that the nervous system is involved in a much larger percentage of cases than is commonly supposed, all physicians treating syphilis should have the equipment necessary for these special examinations. It is only through a more general recognition of the importance of this method of diagnosis that the future holds definite promise of successful neurosyphilis prophylaxis.

## BOOK NOTICES

(Books for review should be sent to Dr. W. H. Deaderick, Associate Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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**SYPHILIS.**—By Loyd Thompson, Ph.B., M.D., Physician to the Syphilis Clinic, Government Free Bath House, Lieutenant-Colonel Medical Reserve Corps, United States Army, etc., 486 pages. Second edition, thoroughly revised, with 81 engravings, and 7 plates. Cloth, \$7.00. Philadelphia and New York, Lea and Febiger, 1920.

The second edition of Thompson's "Syphilis" comes from the press thoroughly revised and considerably enlarged. The chapters on visceral syphilis in particular are much more complete than in the first edition, in fact they have been practically rewritten.

The chapters on the syphilodermata also are much amplified, the differential diagnosis of these lesions being very thorough. For example, it is pointed out that the nodular syphiloderm may be mistaken for lupus vulgaris, lupus erythematosus, epithelioma, acne rosacea and leprosy, and in each instance the points of differentiation are given.

The author states that he has been forced to change his views on certain subjects, for example, the luetin test, which he now considers of little or no practical value, and the section dealing with this subject in the present edition has therefore been greatly condensed.

The term *Spirochete pallidum* instead of *Treponema pallida* has been used throughout the new edition, since, as the author points out, it was the term originally applied to the parasite of syphilis by its discoverer and since this is the term applied by the majority of syphilographers.

The generic term *arsphenamine* is employed instead of the word *salvarsan*.

A feature which in a large measure is new to the second edition is the historical sketch which is found at the beginning of each new subject. This is most interesting and greatly enhances the value of the book. This monograph candidly expressing the views of a single author shows valuable revision in the second edition.

# Index to Current Syphilis Literature

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## Original Articles

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### SOME ACCOUNT OF THE RESPONSIBILITY OF INTENSIVE TREATMENT METHODS WITH REGARD TO THE INCIDENCE OF EARLY NEUROSYPHILIS

BY A. REITH FRASER, M.D., (ABERDEEN)

*Medical Inspector of Venereal Diseases, Union Government of South Africa*

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AT a time when the tendency is all for the clinician to look upon the pathologist as his master and not as his servant or his ally, it may not be out of place to sound a note of warning. In no sphere of work is this fact more in evidence than in the treatment room of the syphilologist. At the present time the world of syphilology is obsessed with the apparently premier position of the pathological and serological finding. The syphilologist is being strangled by the tyranny of the Wassermann reaction. His sheet anchor in diagnosis is the Wassermann, his standard of cure is summed up in the word Wassermann, and his ultimate hopes and fears with regard to the future welfare of his patient is obscured in the misty haze of an empirical and nonspecific potentiality to deviate complement.

The net result of this obsession is a universal tendency to work to a hard and fast program, a subconscious acquiescence to handle the



syphilitic patient *en masse*, a religious determination to plan subsequent treatment after, and not before, the arrival of pathological reports, and a relegation of clinical opinion to a place of subservience and relative unimportance.

#### STAGE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT

When a syphilitic in the stage of localization appears for advice and treatment, surely it is our first duty to plan our treatment procedures with a view to securing for him a future devoid of the risks of relapse, complications, and sequelæ. This is far more important to the patient than an immediate and to him a miraculous disappearance of symptoms. The care and nursing of his central nervous system is then thrust upon us as the sphere of our immediate and imperative duty. In how many cases of primary syphilis is this all-important fact realized and appreciated by modern syphilologists? The steady increase of the incidence of early cerebrospinal syphilis furnishes some indication of what our answer is likely to be.

When the causal organism of syphilis gains entrance, cell reaction occurs around the organism. A lesion may appear at the site of inoculation after a certain period of incubation, but even before this phenomenon is fully established, the stage of generalization has begun. The chancre is the real protective cell reaction, and the more vigorous this reaction, the longer is the generalization of the spirochetes throughout the body likely to be delayed. As the so-called secondary stage appears, the reaction of the tissues against the general infection is demonstrated in the rash, or it may be, the meninges. The entire destruction of the attacking organism by these reactions seldom takes place, and the organism is free to proceed on his way rejoicing. The all-important point to grasp is that the central nervous system is invaded at the time of general systemic invasion. In the absence of a vigorous cell reaction the spirochete penetrates into relatively nonvascular structures, and there may lead a harmless saprophytic existence for years.

While cell reaction is apparent, antibody production is proceeding apace. The general systemic circulation is capable of producing large amounts of antibody very rapidly. The central nervous system, however, is dependent to a very great measure on the general systemic circulation for its antibody supply. When such supply is available,

therefore, the central nervous system is not likely to suffer. A central nervous system devoid of available antibody supply cannot hope to deal with the inevitable effects of spirochetal invasion. When the organism ceases its saprophytic existence and becomes liberated, the immediate-surrounding tissues owing to previous sensitization at the time of infection will react excessively, and the hypersensitive tissues will lend themselves to rapid and wanton destruction. It is clearly the duty of the syphilologist to conserve the antibody supply available for the use of the central nervous system unless he is able to satisfy himself that he has prevented a nervous system invasion, or has killed off every individual spirochete.

#### DANGERS OF WORKING FOR A NEGATIVE WASSERMANN

How then is one to conserve this valuable antibody supply? Are we to look upon the Wassermann reading as a reliable index? Lissner,<sup>1</sup> Umbert,<sup>2</sup> Montgomery,<sup>3</sup> Fordyce,<sup>4</sup> Goldfader,<sup>5</sup> and many others have already sounded a note of warning with regard to the overvaluation of the Wassermann. This warning cannot be repeated too often. To conclude that a patient is cured immediately his serum shows a negative Wassermann reaction is a fatal and unjustifiable proceeding. So also, in the absence of clinical signs is it inadmissible to conclude that a positive Wassermann is the signal for instituting treatment. How often has a cerebrospinal lesion been precipitated by a sudden and enthusiastic administration of arsenobenzene in an otherwise normal individual who happened to show a positive pathological change in his serum or cerebrospinal fluid? Were we to admit the truth, such accidents occur much more frequently than one cares to admit. It is clear, then, that to conserve the supply of antibody available for the central nervous system, it is necessary to promote and conserve the supply of the general systemic circulation from which it draws its main supply. In spite of this obvious circumstance the aim of present day treatment methods is to sterilize the general systemic circulation as quickly as possible, and the result is that the central nervous system is left high and dry, invaded already by spirochetes, and with only its own inadequate intrinsic antibody supply to draw upon. Obviously the important factor is forgotten, that the central nervous system is invaded by the attacking organism coincident with the stage of generalization.

## FAILURE TO PROTECT THE CENTRAL NERVOUS SYSTEM

The cerebrospinal fluid has its source in the chorioid plexuses and possibly in the general serous surfaces of its containing cavities, and is distributed through the ventricles and subarachnoid spaces, having no relation to the perivascular, pericapillary, or perineural spaces. It leaves the subarachnoid spaces of the cranium by passing through the arachnoidal villi into the venous current of the sinuses, the lymph sheaths of the cranial nerves, and in the spinal region the lymph sheaths of the spinal nerves. It has no function of nutrition, and any supply of arsenic which it conveys to the brain and cord from an intravenous source is infinitesimal. Its integral source of antibody supply is the epithelium cells of the chorioid plexuses, together with the lymphocytes which come from the lymphatic vessels of the meninges and nerve tissue. The belief that the brain and cord have no lymphatic system has been abandoned. This supply is altogether inadequate unless supplemented by the antibodies circulating in the blood. This supply reaches it by ultra-filtration. In the same way medicaments such as arsenobenzene reach the central nervous system. The amount which reaches it is therefore infinitesimal, chiefly because the process of ultra-filtration is a slow one, and the ions of the remedy are not such as will readily osmose through the capillary walls.<sup>8</sup> The chorioid plexus and meninges in neurosyphilis become more permeable, and arsenic will reach the intrathecal system in detectable amounts.<sup>37</sup>

From the foregoing it will be seen that the general systemic system is much more readily sterilized than the intrathecal system. Therefore, having already forgotten that the central nervous system has been invaded, the syphilitic's system is rapidly sterilized, the serum Wassermann becomes negative, and the central nervous system is deprived of its main source of antibody supply. Immediately all the spirochetes in the general systemic system are killed off by rapid large intravenous doses of arsenobenzene, the fundamental producing factor of antibody mobilization is removed. The Wassermann therefore becomes negative. In the intrathecal system the spirochete snugly entrenches himself in the relatively nonvascular structures which he has penetrated, and is free from assault by antibody. His saprophytic existence then continues unmolested.

Modern treatment, then, on account of the tendency to work for a



negative Wassermann, plays into the hands of the spirochete. By rapidly sterilizing the general systemic circulation it causes antibody production there to cease. It fails to sterilize the intrathecal system but successfully cuts off its main source of antibody supply. The result, therefore, is that neurosyphilis occurs earlier and more frequently than was the case in pre-arseno-benzene days. The statement that cerebrospinal syphilis occurs more frequently in the untreated syphilitic is open to very serious doubt. Among South African natives where syphilis is either untreated or very imperfectly treated, neurosyphilis is practically unknown. The reason is that the general systemic circulation is never sterilized and the intrathecal supply of antibody is therefore not curtailed. In the case of mercurial treatment, sterilization of the systemic system is slow and imperfect, and the central nervous system is drawing an adequate amount of antibody over a long period. Hutchinson<sup>7</sup> was aware of this fact when he wrote that "During the early periods of syphilis various parts of the nervous system are liable to be attacked by affections curable by the prompt use of mercury."

In the same way when treated with a few consecutive doses of arsenobenzene quick sterilization takes place. If followed for several years by continuous mercury, the nervous system may be successfully sterilized as well. Even if this happy result does not follow, the drug will so control organismal activity and maintain antibody supply that no symptoms will supervene. If the initial sterilization has been too sudden and thorough, the organism may have had opportunity to make his position in the nervous system so unassailable that even the slow absorption of mercury cannot prevent the early precipitation of symptoms. Should such a circumstance occur, we would expect these symptoms to be meningeal in character, and this is what actually happens.

#### EVIDENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT

Instead of making a critical review of our treatment methods which are obviously responsible for the present state of affairs, we have hunted round for circuitous means whereby to cover our retreat. Those of us who have appreciated the serious risk of early cerebrospinal involvement have devised various methods of discovering its presence and of dealing with it in its early stages. This, of course, is

all to the good, but it does not seriously assail the position of what is obviously the fundamental cause—our treatment routine. Such methods of ascertaining the state of matters intrathecal are sharply divided into two groups, clinical and serological. The first depends on exhaustive survey of the patient, and the second on examination of the cerebrospinal fluid. These two methods may be combined, but here again we are under the omnipotent thumb of the Wassermann reaction. Fordyce<sup>8</sup> states the case for the defence admirably when he says: "Modern diagnostic methods and modern treatment controlled by the Wassermann reaction in the blood and spinal fluid, together with other standard spinal fluid tests, have made the study and treatment of syphilis the most absorbing and fascinating subject in medicine. Exact knowledge has largely replaced vague clinical impressions so that we are able to prognosticate the future of a patient affected with the disease with more certainty than in any of the other chronic infections." He goes on to state that 25 to 35 per cent of cases show pathologic changes in the cerebrospinal fluid within the first year of infection. Many of these cases show clinical evidence of intrathecal involvement, while others show none. This is supported by Cornaz<sup>9</sup> who found a lymphocytosis in the cerebrospinal fluid in 35 per cent of cases where the chancre was still unhealed, and the generalization manifestations were not yet apparent.

Clinical evidence of early intrathecal involvement is not wanting. Schoenberg<sup>10</sup> has shown the value of the routine ophthalmologic examination in the primary stage, as well as in all later stages of the disease. He insists that the optic nerves even more than the other cranial nerves must be closely watched through the entire life of every luetic. The occurrence of severe ocular disturbances associated with pachymeningitis localized at the level of the optic chiasma in early syphilis has been noted by Cosse,<sup>11</sup> while other important lines of clinical investigation turn our attention to the condition of the reflexes, and the condition of the circulation. But, as has been pointed out by Hunt,<sup>12</sup> Nonne,<sup>13</sup> and many others, the condition of the pupil is much the most important. Wanner,<sup>17</sup> Beck,<sup>15</sup> and Benario,<sup>16</sup> emphasized the diagnostic importance of eighth and second nerve involvement, and much useful investigation has been carried out by McIntosh, Fildes, Head, and Fearnside.<sup>18</sup>

Early intrathecal involvement, however, may be symptomatic or

asymptomatic, as has been so eloquently pointed out by Klauder.<sup>14</sup> During the stage of generalization intrathecal invasion may be vascular, meningitic, or parenchymatous. The following groups can be differentiated:

*Group 1:* Asymptomatic—total lack of symptoms, but the cerebrospinal fluid may show pathologic changes suggestive of meningeal involvement. This is by far the commonest group. It must not be forgotten, however, that the cerebrospinal fluid may show no pathologic changes in spite of intrathecal invasion. Should the central nervous system fail to react, and the amount of antibody present be nil, the cerebrospinal fluid will appear to all intents and purposes normal.

*Group 2:* Meningeal group—severe headache, insomnia, somnambulance, noises in the head, vertigo, slight, severe or complete deafness, optic neuritis, diplopia and paralysis of the recti muscles, and even opisthotonos.

*Group 3:* Neurothrophic group—acneiform and lichenoid syphilides, alopecia, leucoderma, accompanied by meningeal symptoms and cerebrospinal fluid changes.

*Group 4:* Neurorecurrence group—affections of individual cranial nerves, inequality of pupils, sluggish reflexes, and cardiovascular changes.

*Group 5:* Psychic group—melancholia, irritability, apathy, decreasing memory, moodiness, brutality, and even suicidal tendencies.

The amount of work done on the cerebrospinal fluid in early syphilis has been colossal. Fildes and McIntosh<sup>19</sup> led the way in Britain, and describe the pathologic changes in much detail. Van der Valk,<sup>20</sup> McIver,<sup>21</sup> Carnaz,<sup>22</sup> With,<sup>23</sup> Leopold,<sup>24</sup> and many others describe such changes as lymphocytosis, an increase in globulin, and a positive Wassermann. Artz and Kerl<sup>25</sup> found spirochetes in the spinal fluid in two primary syphilitics out of eleven examined, and Fildes, Roderick, Parnell, and Maitland<sup>26</sup> also demonstrated spirochetes by dark field examination in secondary syphilis. Observations on the colloidal gold reaction have been made by Kellert,<sup>27</sup> Cruickshank,<sup>28</sup> Harvey,<sup>29</sup> Black<sup>30</sup> Warwick and Nixon,<sup>31</sup> and many others, on the Sachs-Giorgi reaction by Kumer,<sup>33</sup> Pincherle,<sup>64</sup> etc., and more recently McDonagh<sup>32</sup> has produced his "Cerebrospinal fluid clock" in connection with his toluene test. The general conclusion of all these workers is that lumbar puncture should never be omitted as a routine in the examination of all



cases of syphilis. Ravant<sup>33</sup> has advocated as the best time for making this examination around the fourth year after infection, and again about the tenth year. We are of opinion that clinical and serological examination should be carried out very much earlier. Many authorities insist that lumbar puncture should form part of the routine in the treatment of every primary luetic, while Carlill<sup>34</sup> regards it as essential to continue periodic spinal examinations at frequent intervals.

#### INDICATIONS FOR LUMBAR PUNCTURE

Indications for lumbar puncture depend on how one regards and interprets pathologic findings in the cerebrospinal fluid. Is a positive Wassermann an indication of implication, cell reaction, or antibody defence? In the absence of symptoms do pathologic fluid changes suggest that treatment is urgently needed, or that the nervous system is successfully holding its own? In view of the successful manner that the untreated African native withstands neurosyphilis, and considering the evidence of lesions precipitated by unnecessary treatment, one is of the opinion that pathologic changes in the absence of symptoms indicate an efficient antibody supply being available for the intrathecal system, and that negative reactions suggest either that the central system has escaped involvement or that it has failed to react, and we cannot tell which. If this is so, why trouble the patient with numerous lumbar puncture examinations? As Lisser<sup>1</sup> so succinctly remarked, once syphilis is diagnosed the fewer serologic tests done the better for the peace of mind of the patient and the physician.

Indications for lumbar puncture may be summarized thus:

- (1) If the diagnosis of cerebrospinal syphilis is in doubt, and syphilis has not been previously definitely established.
- (2) If a syphilitic shows clinical nervous involvement, examination of the spinal fluid will indicate if meningitis is present or not, and if clinically present will indicate its severity.
- (3) In the case of a syphilitic under treatment as an aid to prognosis. Generally, in early syphilis, the case showing that the nervous system has reacted to the infection as evidenced by pathologic changes in the spinal fluid deserves a better prognosis than the case showing no reaction as evidenced by a normal fluid, unless the physician can definitely satisfy himself that the central nervous system has escaped

invasion. This, as a rule, he cannot do with any degree of certainty.

Ravant<sup>33</sup> has emphasized the fact that negative changes in the spinal fluid indicate that no meningeal trouble is brewing, but does not with certainty indicate that the intrathecal system is definitely protected. This we consider a correct summing up of the position. Indeed we would go further and state that negative changes may indicate that the nervous system has failed to react to the infection, and that it is therefore impossible to give a definite prognosis. In this opinion we are supported by the work of Wile and Stokes<sup>35</sup> who conclude that actual cerebrospinal involvement may exist without any of the pathologic changes in the spinal fluid so generally accepted as criteria of intrathecal involvement. Mott<sup>36</sup> theorizes on similar lines and suggests that invading protozoa could make their way to the intrathecal system in the presence of a perfectly normal spinal fluid owing to the absence of an adequate antibody supply. From there they are eradicated with the utmost difficulty because arsenic, mercury, antimony, and other germicides do not pass through the chorioid plexus. In other words the ions of these remedies are unsuitable for ready capillary osmosis.

#### OTHER FACTORS AFFECTING THE OCCURRENCE OF NEUROSYPHILIS

Besides faulty early treatment methods, several factors are of importance with regard to the early incidence of neurosyphilis. These are:

- (1) The patient's resistance;
- (2) The natural protective power of the central nervous system;
- (3) The stage at which treatment is inaugurated;
- (4) The type of infection.

(1) *The Patient's Resistance*.—The severity of the early manifestations seem to influence the tendency to later nervous implication. Whether this is due to a partial inherited immunity or to an increased inherent power of rapid antibody production, the fact remains that the general systemic system is rapidly sterilized, and the nervous system laid bare to later assault. In the natives of South Africa, however, the mild primary stage which is characteristic, and which is frequently absent, is due to a lack of local cell reaction around the attacking organism and not to any inherited immunity. The cell reaction is seen in the generalization stage when cutaneous syphilides

are particularly severe. The antibody mobilized at this period seems to act as a bulwark of defense for the nervous system, which subsequently is never involved to an extent sufficient to produce clinical symptoms.

(2) *The Natural Protective Power of the Nervous System.*—It may be that the nervous system of the South African native has some inherent power of producing a greater antibody supply than the less fortunate white. Nevertheless, should the central nervous system react vigorously to the infection, it will at a future date be less dependent on the systemic circulation for its antibody supply than the nervous system which has failed to react. If, then, a positive Wassermann reaction is evidence of reaction on the part of the central nervous system, a spinal fluid showing such a phenomenon commands a much better prognostication than a fluid which has remained normal. It is irrational, therefore, to treat cases which give positive pathologic changes in the cerebrospinal fluid during the latent stage of the disease, particularly if he has had previous adequate treatment.

(3) *The Stage at which Treatment is Inaugurated.*—If active intensive treatment is commenced before the stage of generalization has set in, and invasion of the central nervous system is prevented, rapid sterilization of the host is called for, and one need not give a thought to subsequent danger to the nervous system. If, however, generalization has started, no treatment can absolutely guarantee protection and subsequent immunity of the intrathecal system.

(4) *The Type of Infection.*—Does the organism of syphilis exist in some form other than the spirochæta pallida? This proposition must be faced, were it only for the purpose of explaining the innumerable varieties of primary lesions and the multitude of variations which may follow them, which cannot be dismissed in a sentence referring vaguely to "the virulence of the organism." McDonagh<sup>38</sup> has described a complete sexual cycle of development of his *leucocytozoon syphilidis*, of which the Spirochete pallida is the fully developed male. The life cycle commences as a spore, and the mature spirochæte produces symptoms. Noguchi<sup>39</sup> has observed that in pure cultures of Spirochete pallida, numbers of minute granules appear under certain conditions. On transference to a passive medium, spiral forms again sprout out. Routh<sup>40</sup> believes that these granules are definite infective agents and are capable of eventually becoming mature spiro-



chetes. Lundie and Goss<sup>41</sup> confirm some of McDonagh's findings, and similar phenomena have been seen by Levaditi. The latter, however, with Marie, supports the contention that general paralysis is due to a special variety of treponema. These workers have done extensive animal experiments to support their belief. Mott believes that the spirochete undergoes certain modification so that there is a biological difference between the spirochetes of general paralysis and those of primary syphilis. He regards a continued supply of antibody as being capable of modifying the virulence of the organism. Kenneth Walker considers that the evidence that the organism of syphilis exists in some form other than the *Spirochete pallida* is overwhelming.<sup>42</sup>

Having failed to correct the primary fundamental factor responsible for the early incidence of neurosyphilis, namely faulty early treatment methods, workers have set themselves to devise and elaborate methods of dealing with the symptoms arising from neglected invasion of the central nervous system. Fordyce<sup>43</sup> declared that the surest way to cure cerebrospinal syphilis lies in the adequate treatment of early syphilis. That is to say, the best cerebrospinal treatment should be prophylactic. This sound advice, however, has been entirely ignored. Far more attention has been directed to symptomatic treatment of intrathecal lesions after the damage has begun. Intraspinal medication after the manner of Swift-Ellis, Ogilvie and others, has been extensively practiced with varying results. Prolonged intravenous medication with and without spinal drainage has also been advocated. Reports of their efficiency or failure are furnished by Fordyce,<sup>44</sup> Nicholson,<sup>45</sup> Levy Bing, Gerbay and Dagnam-Bouveret,<sup>46</sup> Swift,<sup>47</sup> Clark,<sup>48</sup> Lautman,<sup>49</sup> Gaines,<sup>50</sup> Humbert,<sup>51</sup> and many others. Only here and there, however, does one meet with any suggestion of serious prophylaxis, or any probing finger pointing out the weak spot in our early treatment armamentarium.

#### WHERE THE FAULT LIES

Many workers get very near the truth when they suggest that the spinal fluid should be examined in every case of early syphilis as an aid to determining the progress towards cure. Fordyce<sup>52</sup> is a powerful advocate of this procedure, and he states very definitely that the future of every syphilitic depends on the systematic examination of the spinal fluid. Schoenberg<sup>53</sup> also emphasizes the necessity of keep-

ing an early watch for nervous involvement, and lays very considerable stress on the importance of energetic early treatment. The fault of working only for a serologic cure has been noted by Wile and Hasley,<sup>54</sup> but how often are these warnings disregarded? Is it not the case that, in the vast majority of clinics at the present time, whenever the patient demonstrates a negative Wassermann, intensive treatment is stopped, the patient is discharged, and is advised casually to return at intervals "and have a little more mercury?"

The present day methods of treating early syphilis have had no more severe and vigorous critic than McDonagh. His criticism has been both destructive and constructive. He has worked for the protection of the central nervous system, and very early realized that neurosyphilis at the present time is very seriously on the increase.<sup>55</sup> All through his work one can trace the keen desire to sterilize the general systemic circulation and at the same time provide for a sufficient antibody supply for the central nervous system. He has persistently emphasized the importance of clinical observation, a point also insisted on by E. Harrison.<sup>55</sup> This is much more to the point than simply advocating systematic examination of the spinal fluid. It is essential that in every primary case of syphilis we should look upon the central nervous system as already involved no matter what the pathologic findings in the spinal fluid may be. If we find a normal spinal fluid we cannot guarantee definite protection; and if we find a pathologic fluid it can only tell us definitely what we already have taken for granted. As already suggested, examination of the spinal fluid will, if positive changes have been observed, help us considerably in giving a prognosis.

As we have indicated, the initial cause of failure in treatment is the modern method of working to the pathologist's reports, of working for a negative Wassermann or a normal spinal fluid, and of forgetting that our patient's future, and particularly his intrathecal future, is our chief concern. As we have seen, the reactions of the serum and spinal fluid may indicate implication or powers of resistance, and in the absence of symptoms we cannot with certainty tell which. It is therefore of vital importance that the method of wholesale arsenobenzene administration given rigidly and blindly until the Wassermann reaction is negative should be abandoned.

## SUGGESTION HOW TO CORRECT IT

If the case is got before the stage of generalization has set in, every effort should be made to rapidly sterilize the patient. Intravenous arsenobenzene should therefore be employed. If, as McDonagh has shown<sup>56</sup> it is combined with one or two doses of intramine, the maximum amount of the element will be taken up and a maximum amount of protection for the central nervous system will be secured. The value of combining sulphur in the treatment of early syphilis has also been shown by Leoper, Bergeron, and Vahram.<sup>57</sup>

When the stage of generalization is in full swing, our aim should be slow, steady, and gradual sterilization. Sudden sterilization will inevitably deprive the central nervous system of its main antibody supply, and therefore will defeat our object. The nervous system will require all the antibody it can possibly secure, for its own intrinsic supply is hopelessly inadequate. Moreover, if we maintain a steady prolonged supply, the spirochete will undergo modifications and lose its virulence,<sup>58</sup> and should the antibody supply one day fail, the attenuated organism will not find hypersensitive tissues on which to work its will.

McDonagh<sup>59</sup> seems to have covered the same ground when he says: "At one time I examined the cerebrospinal fluid after treatment of all my cases of early syphilis \* \* \* but had to alter my procedure because I found (1) that a negative examination did not prove that the nervous system had not been attacked; (2) that intraspinal injections did not preclude the later onset of a degenerative lesion; (3) that intravenous injections with intramuscular injections of intramine and the intermittent treatment afterwards gave better results. I have also found that a pathological cerebrospinal fluid may be a sign of the patient's protective power against the spread of the organisms, as a destruction of it has so frequently precipitated a degenerative lesion. \* \* \* Much nervous syphilis can be prevented by the routine use of intramine, which prevents arsenic and mercury from exercising a toxic influence on nerve tissue."

The ideal method of treatment, then, is to administer arsenobenzene in such a manner that its absorption will be slow, steady, and gradual. It will then be able to find its way to the intrathecal system, and it will not produce a sudden complete general systemic sterilization with consequent destruction of antibody supply. Intramuscular or subcu-



taneous administration of sulfarsenol over a long period, accompanied by mercurial medication and intramine, is possibly the best treatment procedure at the present moment. Reports of the value of this preparation ( $C_{12}H_{11}As_2N_2CH_2OSO_2Na$ ) have already been furnished by Levy-Bing,<sup>60</sup> Yernaux and Bernard,<sup>61</sup> Doble<sup>62</sup> and others. The antibody supply should be conserved indefinitely by slow, steady sterilization. This may be secured by continuous sulfarsenol, intramine and mercurial treatment over a period of years.

#### CONCLUSIONS

(1) The responsibilities for the increasing incidence of early neurosyphilis rest with:

- (a) The tendency to treat primary syphilitics *en masse*.
- (b) The method of working to a mechanical time table.
- (c) The blind-folded method of working to and for a negative Wassermann.
- (d) Failure to interpret pathological findings in the light of the clinical picture.
- (e) Losing sight of the importance of the central nervous system as regards the patient's future.

(2) Modern early treatment fails in protecting the central nervous system by rapidly sterilizing the general systemic system and thus depriving the intrathecal system of its antibody supply.

(3) The nervous system is invaded coincident with the generalization of the organism.

(4) Nervous system involvement may be symptomatic or asymptomatic. In the absence of clinical signs a normal spinal fluid may indicate the successful overcoming of the organism by the central nervous system or the failure of the nervous system to react. It may also suggest that the general systemic circulation has been successfully sterilized before the intrathecal circulation was invaded. A pathologic spinal fluid may indicate implication or protective power. In the absence of symptoms we cannot accurately interpret the finding.

(5) For the security of the future of the patient the invasion of the central nervous system should be taken for granted.

(6) The occurrence of neurosyphilis is influenced by: (a) the patient's powers of resistance; (b) the natural resistance of the central nervous system and its inherent capacity for producing antibody; (c)

the stage at which treatment is inaugurated; (d) the type of treatment employed; (e) the period over which treatment is carried out; (f) the type of organism responsible for the original infection. In this connection the question of a life cycle of the *Spirochete pallida* must be considered.

(7) Great importance is attached to the value of clinical opinion, clinical observation, and clinical judgment. These should be correlated with careful interpretation of pathologic findings.

(8) The importance of treating each particular case on its merits and as an individual, instead of treating him as one of a series, is emphasized.

(9) Treatment should aim at conserving sufficient antibody for the requirements and protection of the central nervous system instead of defeating one's object by rapid sterilization of the systemic circulation thereby leaving the defenceless nervous system to look after itself.

(10) Antibody supply should be conserved over a period of years. The value of intramine as a protection for the nervous tissues warrants its inclusion in any scheme of treatment.

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## SYPHILIS OF THE HEART

BY HARLOW BROOKS, M.D., NEW YORK, N. Y.

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WHENEVER a pathologist has taken the trouble to make a careful analysis of the cardiac findings in any large number of protocols, even though he rely on the gross findings only he has commonly found himself surprised by the large number of instances in which definite syphilitic changes are present. In such an analysis he is also commonly impressed with the degree to which these specific changes have directly led on to a fatal result.

In 1911, in the course of a study of the cardiac conditions present in one thousand of my consecutive protocols, I, too, was struck with the frequency with which syphilitic changes were found in the heart. As a result I selected from my series of autopsies fifty consecutive cases of unquestioned syphilis and made a study of the cardiac lesions found present in them. These studies at first were in larger part based merely upon such pathological conditions as were demonstrable by the methods of gross pathology, but I have long since verified the type and character of the changes by microscopic studies. Forty-seven out of the original fifty cases showed unmistakable changes in the heart and in over one-half of this series, the death had resulted from disease of the cardiovascular system. Sixty-six per cent of my syphilitic cases, including both well and incompletely treated cases which came to autopsy, were found to have died with or from serious circulatory defects.

It was the original plan of Dr. Carroll and myself to again collect our constantly increasing list of cases and to finally compile a monograph on the subject of syphilis of the heart in all its aspects. Other interests have, however, dominated both of us for the past four years and our additional cases have not yet been classified and analyzed, I shall, therefore, in this resume rely for statistical purposes on papers already published by us on the subject, but I shall for the more final conclusions draw mostly from my wider experience which this class of cases has given me.

There can be little doubt but that the heart is as Warthin asserts to be the case, specifically involved in most cases of acute lues, notwithstanding this quite obvious fact, in some places the heart is still considered as among the viscera of the body least frequently involved by syphilis. The reason for this impression may be perhaps because, up to rather recently pathologists as a class have failed to appreciate that there are other typical lesions of syphilitic nature than the gumma. Warthin has done us the tremendous service of showing for example that areas of the myocardium may be literally swarming with the specific organisms, so numerous as to almost seem to cause mechanical disturbance of so delicately balanced a mechanism, and yet no microscopic lesions were detectable under ordinary methods of study.

Naturally after Warthin's well substantiated statement concerning cardiac lesions not detectable except in sections stained for the specific organisms, one must be very careful in asserting in any case that no specific lesions were present, simply because neither gross nor microscopic changes could be demonstrated by the usual technic. It is also very probable that though organisms were present in many instances their detection failed for technical reasons, for it has been shown that for the successful demonstration of spirochete, the tissues must be fixed within a very few hours after death, a desideratum not possible of accomplishment in most institutions because of the difficulty in obtaining very early postmortems.

Notwithstanding Warthin's evidence to the contrary, I however, still feel from my clinical work, that there are many, very many cases of active lues in which probably no typically luetic changes in the heart are present. I feel authorized in this statement because of the very large material of this nature which I have been able to study in the past eight years, and in which clinically I was unable to demonstrate any indications whatever of cardiac disease and this notwithstanding the fact that the cases had been sent me or to my service largely because of my known great interest in the condition.

I feel also that we must make a very definite distinction, clinically at least, between the heart in syphilis and syphilis of the heart. Notwithstanding my own and the evidence of others in this respect, my clinical and dead house experience compels me to the opinion that there are many cases of syphilis which show also no anatomi-

cal evidence of cardiac involvement, notwithstanding the correct statement that the heart is probably one of the most frequent of the viscera involved in the infection. Of my fifty consecutive cases of lues in five instances the heart muscle lesions were apparently due to secondary changes outside of syphilis. Naturally it was found that the heart muscle was often much involved in such cases but in a good many instances the muscle changes were not in themselves specific though perhaps due to primary luetic alterations in other tissues, as for example, to a coronary endarteritis.

I believe now that we must make also a sharp distinction between syphilis of the heart and the heart in syphilis for the purpose of prognosis. Where acute syphilitic lesions are present in the heart, I am convinced from a very wide clinical experience that a quite favorable prognosis and rapid relief may usually be promised under modern methods of treatment if the primary cause is suspected. If, however, the lesions are not elementarily luetic, even though acute and even though directly secondary perhaps to such a typical luetic lesion as a coronary endarteritis, the prognosis is poor inasmuch as the lesion, be it a brown atrophy, a simple acute parenchymatous myocarditis, or an area of fibrosis or fatty degeneration may not itself be removed by any amount of specific treatment. For this reason I believe that at least in prognosis, no matter how recent the case of infection or the apparent insignificance of the lesion as judged from its symptoms, prognosis must be well guarded until the therapeutic test has shown whether or not the lesion is itself typically specific, and therefore if not of too long standing, removable, or secondary to a luetic condition in which case little or no improvement may follow even the most thorough and persistent treatment.

Another factor which has greatly retarded the general acceptance of the great frequency of cardiac lues had been the relatively great importance given to the subject of syphilitic aortitis. Most of the students of this condition, whether pathologists or clinicians, have contented themselves with a study of the aorta, and lesions of a luetic nature being found here they have assumed, entirely without adequate justification, that all the signs and symptoms present in such cases were therefore necessarily due to the aortitis. Many of the symptoms, we may almost say, most of them, ascribed to syphilitic aortitis, Carroll and I believe we have shown to be due to the concomitant syphi-



litic disease of the heart, for in all the cases of syphilitic aortitis which we have fully examined we have been able to demonstrate definite syphilitic cardiac lesions, especially in the muscle and in the coronary system. The relief of many of the symptoms of an aortitis under specific medication, now generally accepted, we believe to be usually due to improvement of the cardiac lesion, for though it is quite possible to assume that one may stay and bring to a standstill the progress of an aortitis, it requires a most optimistic faith in therapeutics to assume that the mechanical results of the alterations in the aorta may be eliminated wholly by any manner of treatment. It is most difficult on a basis of known physiology to account for dyspnea, tachycardia, precordial pain, arrhythmias and lassitude, typical symptoms so stated of an aortitis, solely on the basis of an aortic lesion, but it is very easy to explain these signs on the assumption of heart muscle or coronary involvement. In brief it is our contention that most of the symptoms supposedly due to syphilitic aortitis are in reality caused not by involvement of the aorta, but that they are due to syphilitic disease of the heart, with which more or less luetic aortitis is, however, usually associated. We would explain the unquestioned benefit which follows specific medication in aortitis on the basis of relief of the cardiac lesions. How can we, for example, account for restoration of a normal rhythm and cardiac force on the basis of removal or checking of the lesions of the aorta? Has any clinician demonstrated by x-ray or fluoroscopic examination any such alterations in the vessel under treatment as might satisfactorily account for the quite remarkable improvement which occurs in the symptoms of the case? As to the checking of aneurysm formation, we have, of course, abundant evidence, but I have been unable to find in the literature any studies of syphilitic aortæ which apparently show that treatment has been responsible for relief on the basis of healing changes demonstrable in the aorta.

It is very difficult for a student of clinical medicine to understand why pathologists and clinicians have both so long ignored the subject of cardiac syphilis, so very obvious and important does the condition become once it is recognized.

It is a very important question as to how early the heart may become seriously compromised in the course of a syphilitic infection. Carroll and I have recorded twenty-four cases in which the cardiac involve-

ment occurred during the secondary period of the disease. Two cases died with a confirmation of the diagnosis at autopsy, the remaining twenty-two cases fully recovered under specific treatment. Two other cases for a short time under my observation, both fully confirmed in so far as modern clinical methods will permit, were apparently unaffected by the treatment and were apparently passing on to an early unfavorable termination when they passed out of our hands. Another case in the secondary stage of the infection died of acute cardiac dilatation while on the witness stand in court, but an hour after a diagnosis of cardiac lues had been made. No autopsy was obtained, but the serological tests were positive and a clean physical examination conducted by a competent physician about a year previous to the time that he was referred to me would seem to confirm my diagnosis of acute syphilitic endocarditis and myocarditis. One of my cases, a young man of about thirty years, died as the result of a perforation of one of the aortic sinuses, before the secondary rash had appeared. Carroll and I have also noted several instances of arrhythmia and tachycardia, two cases of acute pericarditis and several of apparent early endocarditis of the aortic valves in the early stages of syphilis, all of which rapidly and completely cleared up under specific treatment and no other measure.

As a rule, however, the condition is not recognized at least until well into the tertiary stage of the disease, and in a group of three hundred cases reported by us which was specially studied in regard to this point, two hundred seventy-six did not come under observation until late in the third stage. It thus appears that in so far as involvement of the heart is concerned, it begins with the general septicemic stage, progresses with the development of the secondary rashes and continues just as long as any phase of the disease, in any of the tissues, that is, until cure, stabilization or death has taken place.

It is quite noteworthy, however, that in our service, which is largely of a subacute and chronic type of cases (mostly at the City Hospital) most cases appeared in relatively early adult life for treatment. The average age for women was, of the two hundred cases analyzed in this respect, 38.1 years and the average for the men 44.75. We are of the impression not only from this analysis but also from our numerous subsequent cases that women are rather more susceptible to the lesion than men, once they are infected, but this may be

due to the fact that in the early stages men are much more likely to submit themselves to early diagnosis and treatment than women. There can be no question whatever but that the earlier cases come under proper treatment the much less liable they are to develop serious cardiac involvement.

In several instances typically syphilitic cardiac lesions have developed very late in the course of the infection, so late, indeed, that the lesions have been often associated with those of a senility and it thus appears to us that the cardiac lesions of syphilis are precisely similar in point of their appearance to those which occur elsewhere in this disease, they may develop at any time. A somewhat intimate association of cardiac and central nervous system involvement appears to exist.

No data can be given as to the number or extent of lesions present in any case. As a rule lesions are multiple. Indeed one might almost say, in so far as the heart alone is concerned, that the changes are almost always diffuse, but chiefly of the muscles, and that there is a definite tendency to follow the blood vessels in distribution. It will be noted, for example, that in point of origin, nearly all the lesions group themselves about and appear to originate in the blood vessels. In a few cases, however, large areas of heart tissue may be found in which no lesion whatever is evident, in which no generalized aortitis is shown and yet, perhaps, a single point may be seen in which a gummatous process so complete as to almost wholly wipe out all normal structure is present. One case is recalled in which rupture of the heart took place through such an isolated lesion and with very little to suggest syphilis elsewhere in the heart tissue.

#### PATHOLOGY

In my fifty consecutive cases studied at autopsy a coronary arteritis of relatively greater degree than that present throughout the blood vessels of the body at large was found in thirty-five instances. When, however, it is remembered that oftentimes not the entire vessel wall, but perhaps only a very circumscribed portion is so diseased and that thus many hearts may be examined quite conscientiously without finding this particular spot, it may then appear that the coronary vessels are probably involved in practically every case.

Coronary disease as a result of syphilis has been recognized for a



very long time and almost the very earliest studies on arterial disease and on angina pectoris point out the close relationship existing between these conditions and syphilis. It is indeed particularly surprising in view of this fact that the very great prevalence of syphilitic disease of the heart has remained so long inadequately recognized. It is notable in this disease how little, if at all, age plays an apparent rôle in the induction of coronary disease. Five of my most striking and extensive cases of coronary syphilis were below thirty years of age and four others below forty. Two cases (already included) in which apparently every portion of the vessels showed a very active and general arteritis were, respectively, twenty and twenty-two years of age. One of my cases which came for treatment because of a typical angina pectoris, the cause of which was not suspected, was found to be developing a luetic rash which promptly subsided together with the severe angina pectoris under active syphilitic medication. The patient was a young woman of nineteen, previously vigorous and athletic, and she was entirely unaware of the nature of her infection. My experience has been such as to lead me to feel that an unexplained coronary disease or angina pectoris in youth or relative youth should be considered as luetic until this possibility is practically excluded by failure to respond to antiluetic treatment. Gaudier (*Jour. de Méd.*, 1918, xxxvii, p. 29) makes the absolute statement with which I cannot entirely agree, that angina pectoris from sudden occlusion of the coronaries is always syphilitic.

The character of the coronary lesions admit of very great variation. Nothing can be given as a type for the changes since they cover every phase of an arteritis. In several instances the walls of the vessels were found literally studded with minute gummatous foci, in others there was a diffuse endarteritis, in still others a periarteritis, but usually a panarteritis was present. In fact, although in some cases there is a quite typically specific type of inflammation present, in other instances this is not definitely apparent. In one case minute aneurysmal dilatations of the coronaries could be made out.

Another very frequent lesion which I believe to be very closely associated with basic coronary involvement consists in areas of round-cell infiltration about the terminal arborizations of the coronary arterioles. In these areas the muscle tissue has undergone a parenchymatous degeneration with an active hyperplasia of the muscle

interstitium. These changes which we have noted particularly in the very active phases of the disease have been first described by Isaac Adler (Tr. Am. Assn. Phys., May 3, 1898) later by myself, (N. Y. Medical Record, Feb. 24, 1912), and still later by Warthin who was the first to demonstrate the spirochete in such areas. In my opinion as I have studied these lesions they may take on one of three methods of progression, in the less active cases the interstitial hyperplasia continues until all the muscle tissue is replaced and a fibrous scar results, thus accounting for the large areas of diffuse fibrosis which appear in the myocardium in the later stages of the involvement or in instances where round-cell infiltration and the degenerative tendency predominate as would naturally be the termination in the more aggressive instances, gumma form, or a diffuse necrosis occurs.

Gummata of the heart are probably much more frequent than even many pathologists think, probably for the reason that they are usually of relatively small size. In my original fifty autopsies five instances of cardiac gumma were found. Maracek who was one of the first to study syphilis of the heart records ten cases of gumma of the heart in his group of sixty cases (Arch. f. dermat. u. Syph., 1893, xxv, 279). In regard to cardiac gumma, I am strongly of the opinion after a microscopic study of several instances of syphilitic cardiac fibrosis that diffuse areas of extensive fibrosis may have been originated as a gumma which had absorbed to some degree under healthy condition or as a result of a certain degree of treatment for the specific infection and that the resulting fibrosis really in some instances represents a resorbing or healing gumma.

In other cases, however, the fibrosis seems to have followed as a reconstructive process the myomalacia which followed the obliteration of a coronary arteriole either from a complete endarteritis or from the formation in the much diseased arteriole walls of a hyaline thrombus. In still other instances fibroid myocarditis seems to have developed from a diffuse but low grade hyperplasia of the interstitium, as in other low grade inflammatory processes. In the latter case a particular fibrosis was usually found associated with more or less fatty degeneration or fatty infiltration.

Dense patches of fibrosis such as may likely have originated in the first manner described were found present in four out of my fifty cases

and in five other cases the fibrosis was associated with more or less extensive fatty degeneration and infiltration such as probably occurs after the last method mentioned. Six additional instances of apparently definite syphilitic myocarditis were included in my group. Three of my fibroid myocarditis cases had terminated in ventricular aneurysm all of which eventually ruptured, thus causing death. It is my impression that in these last three instances the elemental lesion had been a coronary endarteritis with a resulting myomalacia followed in turn by fibrosis and ultimate rupture through the scar.

Still another fibroid lesion very frequent in cardiac syphilis but also seen in nonluetetic cases is a more or less diffuse interstitial hyperplasia in the papillary muscles, a lesion which results in a restriction of the columnæ earneæ with, of course, more or less obstruction of normal valve mobility.

Many other myocardial changes are found associated in the hearts of syphilitics, for, in my fifty cases, forty-four showed definite gross changes, but in very large part these may not be said to be syphilitic in themselves though in most cases they have resulted from primary syphilitic disease, as the changes in the coronary vessels may lead to parenchymatous or fatty degenerations and probably also to fatty infiltration. Parenchymatous changes probably have much to do with the terminal conditions from which the patient dies and are perhaps thus but remotely associated with the syphilis itself. Brown atrophy was present in seven of my cases. This I also class as not a syphilitic change, but as a probable secondary result either of a general asthenic condition, or perhaps as due again to the lesions of the coronary vessels.

We must not leave unconsidered the probably very important lesions described and demonstrated by Warthin in which although but slight or no microscopic alterations could be demonstrated, sections stained for the specific organism showed areas in which myriads of organisms could be demonstrated. From Warthin's description one cannot but be impressed with the idea that these islands of infiltration may represent early phases of gumma formation or of diffuse syphilitic myocarditis.

Occasionally areas of calcification are found associated with the fibrosis, this probably has no significance outside that present in other fibrotic and degenerative processes.



Endocardial disease in its relation to syphilis has been recognized for a very long time, and yet in many textbooks and monographs concerning endocarditis, while pointing out the frequency of syphilitic aortic endocarditis they mostly entirely fail to state or mention the desirability of specific treatment in these instances. It remained for two distinguished neurologists to point out the efficacy of specific medication in many of these instances (Sachs and Collins, *Tr. Assn. Am. Phys.*, May, 1912.) Endocarditis was found present in thirty-seven of my fifty cases, seventeen of which showed involvement of both aortic and mitral valves. Seven instances of pure aortic disease were in the group and it is probable that these all represented truly syphilitic lesions. No cases of pure mitral disease were found, but in three instances aortic, mitral and tricuspid were all involved and in one case the mitral, tricuspid and semilunar segments only. By no means should all these lesions be assumed as definitely syphilitic. My experience, which has been very much extended since these statistics were collected, has convinced me that valve segment involvement other than of the aortic as a true syphilitic process is very rare and I have never been able to convince myself of the truly syphilitic character of any other endocarditis than that of the aortic segments. One frequently sees, of course, subendocardial luetic lesions in all of the valve rings, but actual syphilitic ulcerative lesions I have never seen except of the aortic segments. I am unable to give a satisfactory explanation for this fact, and several years ago at a meeting of the American Medical Association I stated that I believed that mitral endocarditis of a syphilitic character was probably as frequent as other luetic lesions of the heart. Dr. Richard Cabot at the time asked me if I had ever been able to demonstrate this, saying that though he had looked for a syphilitic mitral lesion for a long time he had never seen one. That was over five years ago, and since that time I have been looking for such a lesion without success. It is true, however, that under specific medication sounds indicating a mitral lesion may be very much altered and heart incompetence associated with mitral lesions in lues may be tremendously benefited by specific treatment, as I have frequently observed, but I have never been able to demonstrate truly luetic lesions other than of the aortic segments at the autopsy table. Brice W. Fontaine (*Southern Med. Jour.*, April, 1918) in an analysis of cardiovascular cases from the Memphis General Hospital states that

he found thirty-seven instances of mitral disease or 28.8 per cent infected with syphilis and in aortic disease, eleven cases (48.5 per cent). The writer after his experience, however, does not feel that Fontaine is justified in the apparent assumption that the mitral lesions were in themselves truly syphilitic, unless it was so demonstrated microscopically.

In very many cases of syphilitic endocarditis the ulcerative lesions may be located only on the periphery of the segments, or on the other hand they may extend up into the arch of the aorta. More frequently than not the process seems however to originate either in the sinuses, about the mouths of the coronaries or on the superior aspect of the segments and to spread downward from that point of vantage.

Before leaving the discussion of aortic endocarditis, I wish to emphasize the admonition of Sachs and Collins urging specific treatment in these cases and pointing out the quite remarkable result which will frequently follow. One must also recall in luetic disease of the aortic valve that the aortic ring itself is often extensively diseased and that it is not merely a question of disease of the valve segments.

In most cases of endocarditis of luetic origin, there is more or less disease of the conus arteriosus and notably of the floors of the sinuses. Disease of these tissues is indeed often present entirely without any demonstrable lesions of the aortic segments and one also frequently sees even extensive luetic lesions in the sinuses entirely without gross disease of the aorta above this point. I believe that modification of the first sound at the base may be found in such cases. The most important and the most frequent site of the luetic process in the sinuses however is about the mouths of the coronaries or the opening of the vasa vasorum and occasionally one finds a little abasis of yellowish tissue raised about the coronary mouth so that it must obstruct the flow of blood into that trunk to at least some degree. Of course in such instances one commonly finds evidences of ischemia either clinically or indicated in the history by arrhythmias, cardiac insufficiency or shown at the autopsy table by areas of muscle degeneration. Several times I have found a little mound of granulation tissue in the coronary mouth almost entirely obstructing its lumen, and which apparently accounted for discrepancies especially in cardiac reserve noted clinically.

While such lesions may be the most striking and obvious ones, in any

case microscopic examination will almost certainly demonstrate luetic changes also in the muscle or in the coronaries lower down so that the old idea, still retained by some that cardiac lues in reality is but a lues of the ascending arch is not substantiated when a complete examination of the heart is made. I am glad to say that I am sustained in this contention by Warthin whose word is of a very startling character it is true, but full appreciation of his absolute accuracy can be assured by an examination of his remarkable specimens, a privilege which I have enjoyed.

One cannot, however, leave the subject of aortic sinusitis without at least referring to the great frequency of aneurysm of the sinuses. It seems probable that this is one of the most frequent locations of early aneurysm though as a rule these aneurysms do not become of large size. Two aneurysms of the sinuses were present in my post-mortem group as compared to eight of other portions of the thoracic aorta, a very high percentage of aneurysm (ten out of fifty cases) in fatal cases of syphilis, I believe. A somewhat suggestive point is brought out, however, in my statistics of aneurysm (postmortem). As a rule aneurysms of the thoracic aorta develop to a diagnostic stage or cause death a considerable time after the inception of syphilis and in my statistics bearing on this point, the average time of detection of aneurysm either at autopsy or by clinical means has been about twenty years after the original infection. Of course with the fluoroscope and x-ray plate much earlier diagnosis is now possible. In the two cases of aneurysm of the sinus mentioned, one developed within six months after the appearance of the primary sore and the other died from perforation of the wall of the aneurysm just as the secondary rash was beginning to become apparent. I wish here to reiterate my statement that I have never seen a syphilitic aortitis without definite syphilitic changes in the heart, and it is my belief that most of the symptoms commonly attributed to the diseased aorta are in reality caused by the cardiac lesions. I believe that relief under treatment bears out this statement.

In my original series of cases the pericardium was found diseased in twenty-eight out of the fifty cases. I do not infer, however, that in all these instances the lesions were in reality syphilitic. Some of them were perhaps mechanical in origin, some certainly secondary to the disease of the coronaries and some were undoubtedly elemen-



tarily syphilitic. I have previously called attention to the lesion of the epicardium which I believe to be quite characteristic of lues though I have also seen it—though rarely—in instances which were neither proved nor thought to have been luetic. This lesion is manifested grossly by the appearance on the membrane of raised, opalescent or pearl colored thickenings which microscopically are constructed of proliferating endothelial cells mingled with hyperplastic connective tissue cells. These patches usually correspond closely to the point of perforation of a terminal arteriole. Carroll and I have observed two clinical cases of acute pericarditis occurring in an early stage of syphilis. Both promptly cleared up, too rapidly we felt to have been merely accidental under active specific medication.

Cases of heart block supposedly due to syphilis have been reported quite frequently. In most instances which I have seen reported the appearance of the block was years after the probable inception of the infection and though a few cases are reported in which recovery took place following specific treatment, in most little or no benefit followed. My assumption is that in these instances the bundle lesion has either been an area of fibrosis, a gummatous process in which complete destruction of cells had taken place, or where the lesion was an ischemic one in which permanent endarteritis or arteriole thrombosis had caused the break in the bundle. Norris and Landis (*Diseases of the Chest*) picture on page 637 a gummatous involvement of the bundle of His, which had caused block. Six cases of block have fallen to my observation, all developing or coming on under observation late in the infection, none of them coming to autopsy. Two were benefited slightly as a result of vigorous treatment with iodides and mercury and with small doses of salvarsan. Larger doses were not employed because of very serious effects which appeared after the first administration. The remaining four cases showed slight or no benefit during the relatively short period of time during which they remained under observation. Most of my colleagues who have had similar cases in their service report to me equally indifferent results but as in my cases the fair assumption is that the cases were old and that the lesion of the bundle was of a more or less permanent character.

One additional case of acute heart block occurring early in the infection has been under my care and was reported in the *Medical Clinics of North America*, Vol. I, No. 3. Briefly, this case developed in a

young and vigorous man of the early twenties who had apparently contracted his lues rather recently and in whom sporadic and irregular treatment (the fault of the patient's habits) only had been administered. The block in this man was not apparent except under slight exercise when it would appear, usually with syncope and a quite typical Stokes-Adams syndrome. The syndrome and its absence at times was confirmed electrocardiographically. Under full dosage of mercury intramuscularly administered together with the iodide of potassium recovery took place so that the patient was able to carry out a great many inadvised athletic and dissipated exploits without any discomfort or return. Salvarsan was not administered for reasons which will be mentioned later, but after the cardiac symptoms had completely subsided the patient was referred back to his regular physician with the recommendation that he then receive salvarsan, and a continuation of the mercury and iodide courses. I understand that the patient did not consider this necessary but up to about a year after his block had been relieved he was entirely well and quite able to do a great many foolish and dangerous things.

#### THE SYMPTOMS

With so wide a diversity of pathologic lesions it must be apparent that there is also a very great diversity of symptoms, since particularly the location of the dominant pathological change determines in the greater part the character of the symptoms which must manifest themselves. In the later stage of the condition only is it commonly possible to precisely locate the lesion and estimate exactly or sufficiently its character. Little diagnostic ability is, of course, necessary for the determination of a heart block, as the symptoms are precisely like those in any other form of block, neither can there be much discussion required as to the symptoms and signs which will be manifest in an endocarditis, valve incompetence being, of course, the rule. It is, however, in the early stages of the disease that symptoms and signs become of particular importance and it is these which have attracted most of our study in so far as symptomatology is concerned.

It is fully recognized that many cases of syphilis, perhaps most, at the time of efflorescence when the mucous membrane lesions and the dermal manifestations are just becoming apparent show a certain grade of fever together with a proportionate acceleration of the pulse

rate. In my opinion these symptoms are rarely absent in cases in which the heart is early involved in the infection. As a rule the temperature is not high, rarely above  $101^{\circ}$ , and the curve shows the usual morning remissions characteristic of other septic processes. Cardiac rapidity is usually proportionately more than the rate of temperature in cases of early cardiac invasion and almost always in our experience there is also a certain degree of arrhythmia. In a series of early cases of lues observed by Dr. Carroll and myself in the syphilitic wards at the City Hospital, through the courtesy of Dr. J. A. Fordyce, we found that many cases showed extra systoles and particularly if the patient was permitted to exercise. There was quite frequently found a pulse deficit together with a very marked variation in the force of the systolic stroke. A tachycardia frequently altogether out of proportion to the temperature was also observed and either emotional or physical stimuli caused a degree of irregularity and tachycardia altogether out of proportion to the grade of the stimulus. Fontaine also notes the presence of fever similar to that in sepsis in many cases. Precordial pain, palpitation, dyspnea, tachycardia, with intermittence, extrasystole or other disturbance of rhythm, more marked on slight exertion together with a soft systole murmur at the apex are frequently seen, all of which we consider when not otherwise accounted for as very characteristic of cardiac involvement even when the history of the infection is denied. In a few cases we have noted a bradycardia, usually of quite short duration, some of these were probably transitory block.

A certain degree of pain in the region of the heart is complained of by many cases and in some instances this is accompanied by Head zone hyperesthesias and by a considerable tenderness on pressure over the sternum. Patients occasionally complain of a sense of discomfort in the region of the heart, as though the "heart were too large for its space" etc. Slight dyspnea is manifest on mild exercise and a considerable degree of apprehension and fear may characterize the mental attitude of the patient.

Auscultation of the heart at this time gives very irregular findings. The heart sounds naturally may show all the peculiarities which are indicated by the irregularities in rhythm and rate. One of the most constant of our findings in the early cases is the presence of a soft systolic murmur at the apex. This murmur is rarely trans-



mitted any considerable distance from the apex. It is usually entirely inaudible at the base.

Grassmann (München. Med. Wehnschr., 1897, xliv) found that dilatation of the right heart was common and that a functional or accidental murmur at the apex was present in 40 per cent of his cases. The murmur is soft and blowing in character, becomes more evident on exercise and is occasionally transmitted to the axilla. There are cases, however, in which we believe that a definite aortic valve invasion is suggested by the presence of a usually soft murmur at the second right interspace, transmitted into the neck and also downwards toward the apex. I have already cited two cases observed by Carroll and myself in which a pericarditis was diagnosed from the character of the friction rub. I do not believe, however, that a clinically diagnosable pericarditis is very frequent in these cases.

Cyanosis is a symptom which in my experience is very rarely present in early cases, but I have observed it present together with very marked dyspnea in two very unfavorable and intractable cases in young women, in both of whom treatment was apparently without avail. Both developed finally frank signs of an endocarditis and died, no autopsies were obtained. One case, already mentioned, developed signs and symptoms of heart block. This is the second instance in which I have seen block in an early phase of the disease. Auricular fibrillation has never been observed by me in early cases, but it is of course very common in old cases.

It must also be stated that in a certain number of cases no symptoms whatever have been noted until suddenly it is found on physical examination that an aortic lesion, a myocarditis or some other pronounced cardiac disturbance is present. In two of our acute cases already mentioned, death was the first known sign or symptom of the condition.

There is one syndrome to which we particularly wish to attract attention, both because of its importance and also because of its frequency both in acute and chronic cases, in fact the symptom of cardiac pain is of so constant occurrence in both acute and chronic instances of cardiac syphilis that I consider it of more importance than any other single cardiac sign or symptom. Fontaine also emphasizes the occurrence of pain. In several instances I have found it is the only symptom complained of and in two instances reported to

me by a colleague it was the only symptom which preceded sudden death. Perhaps in some instances it is caused by minor grades of dilatation, as Grassmann suggests, for it is frequently associated with dyspnea and very slight cyanosis, in more cases, however, I believe that it represents a true inflammation of the heart muscle, a veritable syphilitic myocarditis.

As seen, however, most frequently by internists and rather later in the infection it doubtless usually indicates an angina pectoris. So very frequent are attacks of anginal pain in syphilitic disease of the coronary vessels that I believe that the question as to syphilis should be the first one to arise in any case of angina occurring in youth or relative youth and it should always be considered as one of the high possibilities in every case of angina pectoris. Typical clinical angina pectoris was found by us in 18 out of 200 cases. In most fully developed cases the attacks were typically anginal, coming on in paroxysms and accompanied by symptoms of terror, overpowering fear, ashen countenance and followed by profound prostration. It is usually relieved by the vasodilators, as amyl nitrite, even in the early cases, but unless these patients are correctly treated, that is, given the specific course, the frequency of the attacks and their violence increases, death being naturally a frequent termination.

Pain is by no means limited to the truly anginal cases, but it is one of the most common symptoms of the disease, sometimes it is limited to the precordium, but very frequently it is complained of as reflected into the back, into the shoulder, on either side—most frequently to the left—and, of course, in the anginal types, as going down the arms. More or less pain was complained of in 119 of our 200 cases, analyzed in this respect.

Precordial tenderness best elicited by firm deep pressure over the precordium is present in many cases. At times it is so acute as to cause marked discomfort when the outlines of the heart are being percussed out. This sign was present in 52 instances out of the 200 recorded by Carroll and myself.

Carroll and I observed 10 instances of early clinical involvement of the heart in lues. Later I recorded 14 other instances but since this time though a good many additional instances have been seen by me, they have not been statistically analyzed as they but substantiated previous findings. It is noteworthy, I believe, that while in the service

I saw but two unquestioned cases develop clinically in the large acute specific service in the charge of my comrade, Major Joseph Klauder. I believe that this was because of the fact that in the mobilization camps—certainly this was the case at Camp Upton—the rigid examination and very early and rigorous treatment prevented the development of cardiac symptoms for it must be apparent that signs and symptoms of cardiac invasion only appear in cases which as a rule have either received none or quite inadequate early treatment. I have seen but four cases which failed to respond to treatment when it was pushed as would naturally be the case when the patient was under the care of a competent man. Of these cases that have already been mentioned, two died, the examination being a postmortem one and the remaining two went on from bad to worse entirely unaffected by treatment which was in both instances most rigorously carried out in the hands of competent syphilographers.

I feel that my experience quite justifies the assumption that except in very virulent cases such as every syphilographer occasionally sees the development of a cardiac lesion is an evidence of under-treatment and in our list of cases irrespective of the Wassermann reaction we have insisted on the disappearance of the lesion under proper treatment as a warrant that the signs and symptoms were truly those of luetic disease of the heart, except in the unmistakable cases in which treatment had no effect on any phase of the actively progressing cases.

It appears unnecessary to me to attempt to outline the signs and symptoms of heart involvement in the later stages of lues. They are simply those indicative of the specific lesion present in the case and they differ none at all from those similar lesions caused by other factors as by the rheumatic virus, other septicemias, and so on. I have always insisted, however, that in the diagnosis of these conditions as really luetic that some definite modification follow proper treatment, or that aneurysm be demonstrated clinically, or that the character of the lesions be vouched by postmortem findings. In the light of my present persuasion in regard to the condition I would not, for example, accept the development of a mitral endocarditis in the course of a progressive case of syphilis as luetic for I have never seen this as a syphilitic lesion. As to an aortic one, I should assume under such conditions or circumstances that the process was in the presence of the general infection a specific one, for the reason that I have seen



numerous cases apparently truly cured in so far as we can determine clinically.

Enough, I think, has been said concerning the symptoms of early involvement of the heart in lues to warrant the statement that in no instance should cases of syphilis of any stage be allowed to indulge in heavy strain or exercise until at least they have been brought thoroughly under the effects of specific medication.

It has been very largely assumed, I find, especially by syphilographers who have often been singularly indifferent to the cardiac lesions in syphilis that heart symptoms are rarely complained of by the patients and that the conditions at best were only detected on close physical examination except in perhaps the very long standing or in advanced cases such as, for example, aneurysm. Of the 200 cases which Carroll and I analyzed in this regard 164 *reported for advice because of complaints of circulatory discrepancies*.

The patient suffering from cardiac lues is often placed in a very unfortunate position for the syphilographer is very likely not to examine the heart at all or if cardiac symptoms are complained of, to underestimate the importance of the condition or to assume that it is a lesion within the province of the family doctor or of the internist while the informed internist also is only too likely to assume that the condition is an irremedial one, not to be improved by treatment or to consider that the case demands cardiac treatment only, neither of which position works otherwise than injury to the patient. As Richard Cabot has well pointed out, internists are altogether too likely to content themselves in chronic cardiac lesions in particular, with a simple diagnosis of the mechanism of the probable lesion and make no attempt to question into the all important problem of etiology in which case in many conditions and notably so in lues the possibility of helpful, even curative treatment is lost.

Notwithstanding the fact that many cases of cardiac lues are of long standing, I have observed that clubbing of the fingers and toes is of relatively infrequent occurrence. This is probably due to the fact that such lesions chiefly appear in cases of circulatory defect which have developed in youth and I have seen very few cases of cardiac lues in very young persons. I may also remark here that I have seen almost no cases of cardiac lues in children, probably because I see very few children in my service. It is certainly a question

well worth the attention of the pediatricists but it is not likely frequent since congenital lues is either well treated in youth or its victims die, ordinarily.

Kerley quotes Hochsinger as saying that gummatous aortitis, arteriosclerosis and phleboscclerosis may exist while myocardial and endocardial changes have been observed. (*Practice of Pediatrics*, p. 686.)

A very frequent symptom of cardiac lues which I am unable to explain and yet which is frequently shown is that of insomnia. It was a prominent symptom, almost always complained of spontaneously by our patients in the very high percentage of 25 per cent. It is perhaps allied to the curious symptoms known as "night starts," so frequent in circulatory cases.

In concluding our discussion of the symptoms of cardiac lues I wish to especially point out that they are such as naturally arise from muscle and arterial, that is coronary lesions rather than from disturbances of the valves, pericardium or arch in general except, of course in those instances in which aortic disease appears and here it is commonly the signs rather than the symptoms which first attract attention in correctly observed cases. I believe, however, that the symptoms are sufficiently suggestive of lues in most instances to point to the necessity of a very careful inquiry into the etiology of any cardiac syndrome, especially muscle or coronary disease, when not otherwise adequately explained.

#### DIAGNOSIS

Diagnosis is not as a rule difficult, at least to a presumptive and sufficiently therapeutic degree. Our greatest difficulty in this respect I believe lies with syphilographers in getting them to examine the heart. Otherwise they may permit during treatment many conditions which submit the heart to unjustified strain, although otherwise their specific treatment should be quite adequate. On the part of internists and general practitioners, I find the greatest difficulty lies in inducing them to realize the likelihood and frequency of the condition and most of all not to be content with a simple anatomical diagnosis of the cardiac lesion, but to inquire earnestly into the question of probable etiology. I am sorry to say that there still remains a large class of practitioners so thoroughly therapeutically pessimistic that they deny the possibility of benefit even when the nature of the lesion

has been fully demonstrated. There may even still remain some practitioners who believe that nothing can be done for a syphilitic case in a real curative way. I believe that I have been able to convert several such heretics in regard at least to the cardiac complications of syphilis.

In most internal diseases the history is one of the most helpful diagnostic means, in this condition it is quite otherwise. My hospital statistics showed a positive history in but 30 per cent of the cases and in private and consultation practice the percentage is much lower, in fact in most cases the history designedly or accidentally is misleading in a very positive way, even when one attempts to avoid the unfortunate status of syphilis as a venereal instead of such a contagious infection as scarlet fever or smallpox is, and to direct inquiry as to the skin rashes, sore throat, enlarged nodes and the like.

C. L. Greene (*Journal-Lancet*, May 1, 1917) states that 90 per cent of patients deny a history of lues under routine case taking and one-half of them in the face of positive complement-fixation tests. I have found it much more helpful to direct inquiry along another line primarily. Having determined the existence of a circulatory defect and finding that at least in some respects it corresponds to such as occur in lues, I then eliminate in so far as possible other etiologic factors, then assume lues until it has been disproved.

Too much confidence must never be placed at any time in a negative history, nor must we adhere too closely to traditional ideas in this regard particularly for as is well recognized, a great many cases are found to be suffering from the disease, to show a positive Wassermann and to recover under specific medication, yet who give not one indication of the disease in their history or in their general physical findings. We have, for example, been in the past very largely led to believe that most untreated luetics are sterile. One of my most typical cases who finally died showing extensive cardiac fibrosis, marked coronary disease, double chronic aortic endocarditis, and multiple aneurysms of the thoracic aorta, was the father of twenty-one living children. Cases in which perfectly healthy children are begotten of parents one or both of whom are syphilitic are too frequent in the practice of most men to require special elaboration of this phase further. Most of our older ideas in regard to syphilis must be now reconstructed.



In acute cases, occurring in the very early periods of lues, undoubtedly the concomitant symptoms and signs of the disease are the most helpful, the adenitis, skin rashes and mucous membrane lesions, the falling hair and other general signs and symptoms of the infection. Where possible in this period of the infection the demonstration of the spirochetes from a local sore, from a lymph node, or from a mucous membrane lesion is most certain, for, as all recognize, the Wassermann reaction in this period of the infection is frequently negative.

In every case, of course, the diagnosis is divided elementarily into two parts, the diagnosis of the general infection and the diagnosis of the cardiac involvement. In the early stages the latter is frequently the more difficult but the appearance of cardiac irregularities without a previous history of them, or of dyspnea, especially pain and tenderness in the precordium or the presence of the soft murmur at the apex, these are particularly important if previously not present. Even more important is the existence of precordial tenderness and of cardiac pain of almost any character, especially if these signs and symptoms are accentuated by mild exercise or perturbation. Other etiological factors capable of causing such a finding being absent, I feel that our diagnosis on any other assumption must be by the exclusion of lues as the basic factor. Several instances of the sudden and unexplained onset of the signs of an aortic ring endocarditis has also made the diagnosis one primarily of *exclusion* of syphilis.

It must always be remembered that while perhaps the diagnosis of the existence and type of the cardiac defect may be the more difficult, the diagnosis of the lues is by all odds and from every standpoint the more important. I feel that in every case where the possibility of syphilitic infection exists, this should be the primary assumption until it is disproved, so very important is the earliest possible introduction of specific treatment at least from the standpoint of the heart lesion.

There can remain now but very little question as to the Wassermann reaction being the most helpful diagnostic measure in all old cases in which cardiac complications have arisen. In so far as our observances extend it seems that the Wassermann reaction is correctly positive in most cases of circulatory syphilis, but by no means in every instance. In some cases the reaction may be activated by the administration of a few doses of salvarsan, though for this purpose

most correctly prefer the mercurials. A negative Wassermann must, however, never be taken as conclusive when the aspect of the case otherwise indicates its probably luetic origin, the reaction may have been slow in its activation. I have known the positive to be returned only after some months of treatment and in cases in which the specific organism was subsequently demonstrated at postmortem or in which, better still, the therapeutic test gave such brilliant relief that no reasonable doubt could exist as to the correctness of diagnosis.

The demonstration of concomitant lesions of a highly suspicious character may also be of great assistance in diagnosis. Such evidence comprises tibial nodes, enlargement of the lymph nodes, chronically inflamed joints, suspicious scars upon the throat, on the tongue or genitalia and the evidences of old dermal lesions otherwise unaccounted for. There seems to be a special likelihood of lesions of the central nervous system being associated with those of the circulatory system, this we found to be the case in 20 per cent of the late cases collected by us and associated lesions of one character or the other were elicited in 111 of our 200 cases. Of course the association with aneurysm is almost finally conclusive as to diagnosis.

Sears (Boston Med. and Surg. Jour., June 16, 1910) believes that syphilis should be suspected, however, in apparently healthy patients who as a result of overwork or some sudden exertion, suddenly develop urgent cardiac symptoms. These symptoms consist of tachycardia accompanied by great anxiety and mental distress, or by the usual signs of myocardial insufficiency. Severe nausea and vomiting may be early symptoms. A striking feature of these cases is their failure to respond to the ordinary cardiac tonics.

There are certain cardiac lesions which one is quite justified in considering as syphilitic until the contrary has been proved to be the case. One of the most certain of these is a pure aortic endocarditis, another is any unexplained cardiac lesion occurring in relative youth and which gives rise to the symptoms of an angina pectoris, and even most cases of adult, though not of senile angina. Aneurysm and the signs of an aortitis except in the senile are also most suggestive points of diagnosis. Unexplained cardiac pain and sensitiveness are also strong presumptive signs when not otherwise explained. Cabot would classify as "probably syphilitic" many instances which he could not otherwise account for and Breitman (Berl. Klin. Wchnschr.,

Sept. 25, 1912) believes that many supposedly rheumatic heart affections are in reality syphilitic in origin. He points out particularly that these hearts fail to respond to the ordinary cardiac stimulants, to which I would add the proviso, until the cases have been first brought under specific medication.

Finally there remains to be considered what I believe to be the most important of all methods of diagnosis in probable cardiac syphilis, namely diagnosis by the therapeutic test. In accuracy it is but little behind diagnosis by biopsy or at autopsy. It has the tremendous advantage of giving not only relief, but often final benefit in cases in which cardiac lesions may not necessarily be wholly syphilitic as it is in cases in which, for example, a rheumatic mitral disease is complicated by a luetic muscle or aortic valve lesion. Unless very carelessly given or in persons who are abnormally sensitive to the drugs employed, it does no harm, and in positive cases often the saving in time is of critical importance. One of the most striking results in most cases of cardiac pain due to syphilis except in well developed cases of angina, is the quick relief of the pain and cardiac tenderness. It is to be employed in every case of doubt certainly, and its manner of application should be precisely as would be the case in which a regular treatment was being introduced. There is little doubt but that the general value and accuracy of the Wassermann test has unfortunately reduced the frequency with which the therapeutic test is now employed in not only cardiac, but other forms of syphilis as well, yet it is one of the most accurate, definitely selective, and beneficial methods of diagnosis, and it is most exceptional, that it does harm. As has been pointed out it is beneficial even in many instances in which the syphilis is not the whole factor concerned in the cardiac phase of the case.

#### PROGNOSIS

There are very few internal conditions in which we can truly say that the dominant factor in prognosis is determined by the character and time of the medical treatment given. This is one of them beyond any doubt. Where early diagnosis is followed by prompt and efficient treatment, the prognosis is extremely good even in cases which manifest anginal symptoms and signs. Often in these early cases the entire cardiac picture is wiped from the symptomatic slate by a few doses of mercury or salvarsan. This does not, of course, indicate that



anatomical cure has resulted, or permit the suspension either of specific treatment or of the precautions which are so essential in practically all cases of circulatory crippling. There are, however, instances in which in these acute cases no effect seems to follow medication, no matter how skilfully administered, either as regards the cardiac complications or on the general infection. I have seen apparently hopeful early cases of syphilis show no benefit whatever under the skill of most competent men. Similar cases have probably fallen to the lot of most practitioners. There are also instances in which notwithstanding the fact that the general manifestations of the disease appear to subside under the specific treatment, no obvious benefit as to the cardiac lesions follows. It is, of course, possible that in these particular examples the cardiac lesions are not specific but concomitant, but I feel that this assumption is quite unnecessary since we see the same conditions pertaining with lesions in other organs, notably in the central nervous system in which a progression even of the syphilitic disease may continue even though the evidences of general infection subside under treatment.

Even taking into consideration these infrequent refractory cases, they are all rare in early instances and in most cases the relief of the cardiac disease is quite as brilliant a therapeutic achievement as the removal of the rash and much more so than the cure of the mucous membrane lesions. There is no more beautiful and encouraging result to be obtained in the field of internal medicine than is very frequently that in properly managed cases of early cardiac lues.

Greene states that he has seen many cases of excellently maintained cardiac reserve over long periods even in men doing hard labor. One of my cases who has five times entered the City Hospital in decompensation because of a much dilated and hypertrophied fibroid heart with undoubted coronary disease, attacks of anginal nature, believed to be caused by dilatation, as well as by a large aneurysm of the transverse arch, has, since leaving the occupation of longshoreman on our recommendation, worked, except during his periods of decompensation, as a truck driver. Thus far he has not failed to recompensate under mercury, iodides and digitalis. He has now been under observation for a period of nearly six years since the original diagnosis when these conditions were found and when he first received specific treatment. He has not borne salvarsan well, so his treatment has since been almost

solely with iodides, mercury and from time to time rest and digitalis. The prognosis in cases which have relapsed after marked or reasonable improvement is, however, not usually good. Disturbances of rhythm particularly which fail to show early and definite improvement under treatment rarely justify a good prognosis.

Some of my early cases have now remained under observation for a period of eight years, and I believe the results to be a final cure. This again, however, depends very much on the skill and persistence of the therapist. If in this stage the infection is cured, then I am quite certain that the cardiac lesions are also cured, and I would even go so far as to say that I now believe that cardiac cure has taken place in some instances in which the Wassermann has not been permanently negative.

Quite naturally in long standing cases in which islands of adult fibrosis have formed in the heart muscle, in which fibrous and calcareous deposits have limited the stream in the coronaries or in which so extensive destruction of myocardium has taken place that fibrous replacement has been extensive, a complete cure of the cardiac lesion in so far as cardiac physiology is concerned is of course impossible, even though the infection itself may have been completely eradicated. No further argument would appear to be necessary urging early treatment in this infection.

Many chronic cases at first show startling benefit, cardiac compensation is restored, pain and dyspnea completely disappear, and yet the reserve of the heart has been so cut down that increased demand on the heart can be met to but a limited degree. In yet other cases long periods of great benefit become apparent during which not only the regular but also the reserve power of the heart appear to be restored, and yet a relapse takes place sometimes after months of apparently normal conditions. I was at first inclined to be very much discouraged over these relapsed cases since never does one achieve such brilliant results or so prompt in those cases requiring second and third stages of treatment. My more prolonged experience with the condition has, however, led me to feel more optimistic than was the case after my longest cases had been under observation but two years. Permanent injury to the heart must, however, be assumed to have taken place in late cases, even though prompt response to treatment

and apparent cure occurs. In most cases at least one is able to add months or years of tolerable comfort in apparently hopeless patients.

#### TREATMENT

Treatment resolves itself primarily under two heads, the treatment of the specific infection and that of the cardiac defect. Of the two the former is by all odds the more important, in fact this is the one indispensable thing to be considered in every case. Failure to adequately recognize this fact is certain to bring discredit in every instance. On the other hand even in the acute instances the clinician must not fail to remember that the heart condition itself must be fully considered in every case, though in the acute instances this simply resolves itself into a recollection of the crucial importance of rest in actual or apprehended decompensation until such time as the tissues have been brought fully under the influence of the specific treatment.

The management of the acute cases is relatively simple. Patients showing irregularity of action, especially if there be a pulse deficit or if a murmur be present or if pain be present, must be absolutely confined to bed and kept just as quiet as possible until such time as the patient is brought fully under the effects of the specific drugs. During this period it is not only usually useless but unwise to give such drugs as digitalis, atropin, strophanthus and the like for the reason, in the first place, they have but little effect and secondly because it is not stimulation but rest that is needed. At this period before the case has been brought under the effects of the specific treatment, exercise of any kind is attended with considerable danger, from an acute coronary thrombosis, perforation of an ulceration or conceivably from an acute block. As a rule such drugs as digitalis given at this period are absolutely without effect, or the effect produced is atypical and inadequate, and I believe that all drugs of this nature are very unwisely prescribed. On the other hand, morphine may be used to check the pain and perturbation or bromides to quiet nervousness in case pain is absent or slight.

Iodides are in my opinion almost wholly without effect in these cases and the drug on which I have the greatest reliance is mercury, preferably given intramuscularly, though in some cases it may be best given by mouth or by inunction. The purpose is to bring the system under the effects of the specific just as promptly as possible. My own



experience has been against the early advisability of using salvarsan or other forms of intravenous arsenic in these cases. In several instances very serious collapse has apparently resulted and I am strongly opposed to its use in acute cases with cardiac involvement before the case has been thoroughly brought under the effects of mercury. I then also advise that because of the cardiac involvement it be given at first in small dosage gradually increasing, but our main reliance must be upon the mercury.

After the symptoms have been brought under the effects of the specific, no objection can be urged against the use of digitalis or strophanthus, atropin, etc., but as a rule it will not be found necessary to resort to them and if so it will be found that they have a much more satisfactory effect in smaller doses than before the specific has been given.

Care must be taken for a considerable time after the relief of all circulatory symptoms before the patient is allowed to return to full work or strain, physical or nervous, and it must be understood that permanent results are only reached when the specific cure is fully carried out. As a rule under such circumstances, no special cardiac medication will be necessary, and in so far as I may judge from the cases under my charge, the cardiac cure is complete if the general infection is eradicated.

Throughout the course of treatment it is very important that at relatively frequent intervals thorough fluoroscopic and physical examination of the chest be made, not only for the purpose of discovering aortic aneurysms, but also so that we may early detect cardiac aneurysm, dilatation of the chambers, or at times, coronary aneurysm, congestion of the lungs, etc.

Results of so definite and final a nature must not be expected in long standing cases, even though in an old case of lues, acute cardiac symptoms or signs have but just appeared. It must be assumed that nonetheless the cardiac lesions are of long standing. Any other assumption, I feel, will sooner or later bring disappointment and disaster. Here, however, if need be, digitalis or other cardiac stimulation may be given if thought necessary, but as a rule poor results only will at first attend the use of these drugs. Rest, preferably in bed, is, of course, indicated at least until the specific drugs have been given for several days and in case of an aortic endocarditis, angina pectoris,

marked irregularity or in aneurysm either of the heart or of the aorta, rest should be maintained for a long time and normal exercise should be resumed only slowly and as it were experimentally. As soon as the case has been brought well under the effects of the specific drug, the usual methods of cardiac management as in any case with a like lesion of the heart may be instituted.

Some evidence led Carroll and myself to conclude that "interrupted or inefficient treatment establishes an immunity or resistance on the part of the lesions against the specific drugs employed. Hence the importance of vigorous and carefully systematized treatment." (The treatment of Heart Involvement in Syphilis Based on a study of 300 Cases, Jour. Am. Med. Assn., Oct. 12, 1914, lxiii, pp. 1456-1461.)

As in the acute cases, so here also, I do not advise the early use of the intravenous forms of arsenic and I believe that in this respect we should still adhere to the early suggestions of Ehrlich. I have certainly had some very uncomfortable moments on cases in which I attempted to introduce early specific treatment by these arsenical preparations. While I have actually lost no cases, in several instances I have been greatly frightened, notably in three cases of heart block, in two of which death was thought to have taken place, but through vigorous measures we saved the cases finally. I am not anxious to repeat these experiences. Candor compels me to admit that several of my colleagues have not met with these unfortunate results and that they have successfully used these preparations with no bad result—as yet.

My custom has been to give mercury intramuscularly, perhaps as an inunction, following it by a course of the iodides forcing the drug to the limit of its tolerance, meantime observing every necessary circulatory precaution. After a second course of mercury, which I believe should be also forced to the point of toleration, I believe it safe to take up the use of the intravenous types of arsenic. I believe that the best results are reached when the form of mercury administered is varied from time to time, but in the chronic cases there is no doubt whatever but that mercury and arsenic alone fail to produce the final or satisfactory results which are reached when the iodides are also given.

There is no question whatever but that in practically all long standing cases and with these I include also cases of apparent acute cardiac

disturbance which have developed in the course of old syphilitic infections, the treatment must be a protracted one. Even when no circulatory signs or symptoms are present I am convinced from my past experiences that the specific treatment must be repeated at intervals or the signs of circulatory incompetence, though perhaps in a different form will return and I have never had in old cases anything like the startling improvement usually manifest in new cases when the secondary treatments were obligatorily introduced later on.

Nonetheless it will frequently happen particularly with hospital cases that they will cease treatment and pass out of sight from time to time. They are almost certain to return to our service sooner or later. Notwithstanding the very much less favorable prognosis in such cases, vigorous methods will give their reward. So definitely has this been the case in the experience of Carroll and myself that we look for return cases at the hospital as soon as we go on service.

After cases have been thoroughly submitted to the specific treatment they will then be found to respond in a quite normal manner to the usual forms of heart stimulation.

Except where physicians feel themselves entirely qualified to undertake the specific treatment of the cases it seems wisest for the internist to work in association with the syphilologist. Such has usually been my custom for those thoroughly familiar with the use of mercury and with the various intravenous forms of arsenic in particular are more likely to secure good results. As a rule I have felt that better results have been accomplished when the drugs have been administered in courses rather than continuously and when the form of the drug has also been changed from time to time. As regards mercury in particular, that which I have used with most success has been the salicylate given intramuscularly, the bichloride in some cases has acted well and in the form of inunctions both calomel ointment 10 per cent and the familiar Blue Ointment have been most employed. For those cases which tolerate vapors better I have used calomel vaporized in the usual manner. I confess that I feel much more secure in these cases when working in conjunction with a good syphilologist, but there are very few of these sufficiently in touch with cardiac diagnosis and management to be entrusted with the full charge of any case of this type.



## CONCLUSIONS

Syphilis involves the heart with great frequency both in early and in its later stages of the infection.

Syphilitic lesions of the heart may involve the pericardium, the myocardium, the endocardium, and the conus arteriosus. The most frequent lesions apparently originate or progress about the terminals of the coronary system, and they are located for the greater part in the myocardium.

Any form or stage of syphilitic lesion except chancre may be found in the heart.

Cardiac involvement may appear very early in the infection when it may terminate fatally, it may long remain quiescent or first become apparent late in the disease.

The signs and symptoms of syphilis of the heart are simply those resulting from the particular lesion present and often develop few or no definite clinical characteristics aside from their association with a history of infection, the Wassermann reaction, and the relief of symptoms and signs under specific treatment.

Ordinary methods of cardiac treatment fail to give relief of the signs and symptoms of the disease unless combined with specific medication.

Syphilis of the heart may in most early cases be cured by specific treatment. Late cases can be much improved, entirely relieved or perhaps cured by specific treatment.

Diagnosis rests chiefly on a history of infection, concomitant signs of it in other tissues, the positive Wassermann reaction, and notably on relief under specific treatment.

Successful treatment in any case rests on the recognition of the cause of the disease.

## CONJUGAL SYPHILIS OF THE NERVOUS SYSTEM\*

BY ALFRED GORDON, M.D., PHILADELPHIA, PA.

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IT WAS in the year 1887 that the first authentic observation concerning conjugal paresis was placed on record. Acker<sup>1</sup> and Ziehen<sup>2</sup> report cases of two couples who died from parietic cachexia. In the following year Mendel,<sup>3</sup> besides confirming the observations of the two former authors with regard to paresis, brings forth also cases illustrating the occurrence of tabes in women whose husbands were parietic and vice versa. Since then a large number of cases have been published by French, German and American writers, showing that when one member of a married couple is suffering from paresis or tabes the other may also become affected with one of these two maladies, but not necessarily with the same form of the syphilitic disease. From 1887 to 1900 so many cases have accumulated in the literature that *à propos* of a discussion on conjugal tabes before the Paris Neurological Society by Souques,<sup>4</sup> Babinski remarked that when he finds himself in the presence of a married tabetic he invariably and systematically looks for symptoms of the disease in the other spouse. The same opinion was then expressed by Dupré, Marie, Dejerine and Gilles de la Tourette.

Further observations have shown that not necessarily tabes or paresis will develop, but also slight or even very slight symptoms may be present in one member of the conjugal couple when the other is affected with either of the two serious diseases. They are so-called "formes frustes" of tabes or paresis. Such were the observations reported by A. Marie.<sup>5</sup>

It was further observed that not only the wife will eventually develop the disease from which the husband has been suffering for years, or *vice versa*, but also the children living with diseased parents may become either tabetic or parietic. Such observations we find in the work of Bernstein and Artemoff.<sup>6</sup> In one case two sisters and in another a sister and two brothers developed paresis.

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A. Marc<sup>7</sup> also records the histories of three families, in every one of which several members were paretics. Twenty-five such cases were observed by Raviart, Hannard and Gayet<sup>8</sup>. During a period of eight years I have been collecting cases of syphilitic affections of the nervous system which developed during conjugal cohabitation and I have succeeded in obtaining full records of 32 such individuals. Their histories are given in the present contribution.

The following chief features were investigated: The onset of the affection in each parent and the date of its appearance in the second parent after the malady had existed in the first parent a certain number of years; the onset of the syphilitic infection in the original parent; finally the Wassermann reaction. It can be seen that not only tabes and paresis in their classical forms were present, conditions which were found by the majority of observers, but also other forms of nervous manifestations referable to the brain and spinal cord or to both. Thus in my series five such cases were observed. Comparing the date of appearance of the first symptoms of tabes or paresis in the second parent with that of cerebrospinal symptoms of nontabetic or nonparetic character in the same parent, we find that in the largest majority of cases the date of appearance of the former is much later than that of the latter. The number of years of the former ranges between seventeen and five years after marriage. As far as possible an effort was made to ascertain the medical histories of the wives prior to their marriage or of the husbands whose wives became diseased first. It is interesting to note that in the majority of cases of tabes or paresis symptoms appeared many years after the beginning of conjugal life. However, in cases in which second marriages occurred or marriage relations after separation from the first wife were maintained, the appearance of syphilitic manifestations was earlier in the second wives than in the first ones. It is difficult to find a satisfactory explanation for this peculiar and apparently paradoxical phenomenon.

The next interesting observation concerns the transmission of nervous syphilis to men heretofore healthy through the intermediary of women who developed syphilis of the nervous system many years after their first marriage to men having a positive Wassermann reaction. In one case, for example (4a), the husband had taboparesis at thirty-eight. His first wife lived with him five years. She later



married a divorced man, presumably healthy, whose first wife brought him two healthy children. Eight years later both showed symptoms of tabes. In another case a married woman, who after having had three healthy children with her husband heretofore healthy, became the mistress of a married man whose Wassermann reaction was positive and who when examined at fifty-one showed signs of paresis. After five years of this double life she developed symptoms of tabes and her legitimate husband signs of cerebrospinal syphilis, with a positive Wassermann of the spinal fluid. In still another example (Cases 7a and 7b) two men, one single and the other married, heretofore healthy, had prolonged relations with one woman, who began to show symptoms of tabes one year after the death of her husband, who had a chancre one year before marriage. The single man, five years after continuous relations, commenced to show symptoms of cerebral syphilis (Wassermann positive of serum). The married man eight years later presented evidences of tabes, with a positive Wassermann of the spinal fluid.

Nervous syphilis may be transmitted not only to individuals who lead an intimate conjugal life, but also to persons who live constantly together in the same dwelling, such as close relatives who may come in daily contact with each other for years. In the case of 9a, for example, we see that she is twenty-two years old, always lived with her oldest brother, J. P. (case 9), who at forty showed symptoms of paresis and whose two mistresses had respectively symptoms of cerebral syphilis and tabes. This sister, whose parents were healthy and left five healthy children, herself a music-teacher and of excellent habits, commenced to show symptoms of cerebral syphilis at twenty-two, with a positive Wassermann of the spinal fluid. In case 10b, a young man, aged twenty-three years, never before had sexual intercourse. His father, a physician, married at twenty-seven and a year later the son was born. The father formed a liaison with a woman whose blood and spinal fluid gave a positive Wassermann reaction. He developed taboparesis. The son presented at twenty-two symptoms of cerebral syphilis, with a positive Wassermann reaction of the spinal fluid.

The present study indicates also another important feature from a diagnostic standpoint. It shows that there were more positive Wassermann reactions of the spinal fluid in the second party, who

developed nervous syphilis years after the beginning of conjugal life, than in the first party of the married couple (10 to 7). Conversely there were fewer positive reactions of the blood and spinal fluid combined in the first than in the second group (2 to 5). Moreover, in the two cases mentioned above (9a and 10b) in which there were no sexual relations, but merely cohabitation (sister and son, respectively), the Wassermann reaction was positive only in the spinal fluid. This information is instructive from the standpoint of diagnosis, as it seems that one must not be content with a serum test in cases of individuals who have been living together for years and who present symptoms suspicious of an involvement of the central nervous system. A single such test may be deceiving. The foregoing observation points rather to the advice that in all such cases it is pertinent to commence with a biological test of the spinal fluid; if the latter is found positive (which is most frequently encountered) a blood test could be entirely avoided. It is only when the former is negative that the latter must be resorted to.

The conclusion which can be drawn from the present study is that conjugal syphilis is more common than it is generally believed, that it may be present not only in the wife after she has cohabitated with the man for a number of years, but also in every other individual (sisters or brothers) living in the same dwelling with the affected person after a number of years. In the latter case the question of hereditary syphilis was entirely eliminated in the present study and has no bearing upon the subject under discussion. The few such cases in my series developed their affection long after the fathers became infected.

A few problems remain to be solved: by what mechanism is the infection transmitted to the wife and why the symptoms make their appearance in the latter so many years after she had cohabitated with the man. The query is particularly difficult for solution when it concerns relatives other than wife or husband, namely, persons that did not come into intimate relations with the original carrier of the disease. Another problem which requires discussion is why in some cases the wife develops tabes, in others paresis, and in still others cerebral syphilis, also why in some cases she has the same form of nervous syphilis as her husband and in others a different form. Is it because in accordance with Edinger's exhaustion view,

one fatigues more his spinal axis and will develop tabes and the other overfatigues more his cerebral portion of the nervous system and will develop paresis? Finally are these special localizations controlled or influenced by hereditary conditions which present a locus minoris resistentiae to the invasion of the syphilitic virus? These are all problems which in the light of our present knowledge cannot be solved categorically, but are all important subjects for consideration and reflection. It must be borne in mind that not only tabes and paresis, as it was formerly believed, but also all forms of nervous syphilis may be encountered in the other partner of the conjugal couple. Special emphasis deserves the occurrence of such conditions in sons and daughters who live with their affected parents irrespective of hereditary transmission of syphilis.

Although during a period of eight years the writer has succeeded in collecting only 32 cases, a fact which may lead to the view of the rarity of conjugal syphilis of the nervous system, nevertheless their occurrence is sufficiently striking to call serious attention to the gravity of the problem. A detailed account of the cases is as follows:



NO. NAME, OCCUPATION, AGE AND INCIDENTS OF MEDICAL LIFE	DIAGNOSIS	ONSET OF SYPHILITIC INFECTION	WASSERMANN TEST
1 B. A., husband, bookkeeper, aet. 51	Paresis, unequal pupils; Argyll Robertson; characteristic speech; expansive delusions.	at the age of 25 years	+spinal fluid
1a M. A., wife; aet. 40; married at 20; two miscarriages; one child living and well at the age of 17.	Paresis; first symptoms at 35; depression; speech characteristic; Argyll Robertson; K. J. ++		+spinal fluid
2 A. C. husband; peddler; aet. 45	Syphilitic myelitis at 27 years, (Paraplegia; K. G. ++; toe phenomenon; bladder and rectum involved).		+serum +spinal fluid
2a S. C., wife; aet. 41; married at 18; five children; two imbeciles; one epileptic.	Tabes; first symptoms at 35 (shooting pain in legs; loss of K. G.; Argyll Robertson; ataxia; loss of Achilles' reflex).		+spinal fluid
3 O. B. husband; aet. 47; married at 27; clerk in law office.	Paresis; first symptoms at 43 (depression; small and unequal pupils; tremor of lips; characteristic speech; K. J.). Tabes, (loss of K. G. and of Achilles' reflex; Argyll Robertson; ataxia).	at 20 years	+spinal fluid
3a C. B., wife; aet. 39; married at 25; 3 miscarriages; no living children; left husband before he showed symptoms of paresis; lived with another young boy of 19 presumably free from syphilis; became pregnant one year later; child living and healthy; eight months later commenced to show evidences of Tabes; young man left her, and his further history could not be traced.		At the time she left husband, her serum and spinal fluid were negative to Wassermann & Lange's test.	+serum +spinal fluid
4 L. M., husband; bankteller; aet. 38; married twice, at 29 and 35.	Taboparesis, (Expansive K. J. lost; pupils unequal; optic neuritis; history of gastric crises and of lancinating pain in limbs; tremor; parietic speech).	Infection at 20	+spinal fluid

NO. NAME, OCCUPATION, AGE AND INCIDENTS OF MEDICAL LIFE	ONSET OF SYPHILITIC INFECTION	DIAGNOSIS	WASSERMANN TEST
<p>4a First wife (A. M.) married at age of 19; one miscarriage; one living and healthy child; separated at 24; married a divorced man of 30, presumably healthy, whose first wife brought him two healthy children; eight years later both showed symptoms of tabes.</p>		<p>Tabes (loss of reflexes; narrow pupils; Argyll Robertson; ataxia).</p>	+serum
<p>4b Second wife (N. M.) married at age of 26; two miscarriages.</p>		<p>Headache (persistent and with paroxysms of unusual severity; the K. G. ++; No other symptoms.)</p>	+serum
<p>5 J. O'B; teacher; aet. 45, married twice.</p>	at 20	<p>Cerebrospinal Syphilis (Headache; palsy of cranial nerves; memory poor; K. G. unequal; sphincters disturbed).</p>	+serum and +spinal fluid
<p>5a First wife (L. O'B.); married at 20; heretofore never ill; one miscarriage; after which separated (five years after marriage); married again a year later; one child apparently healthy; 7 years later symptoms of Tabes; husband healthy.</p>		<p>Tabes (Loss of reflexes; ataxia; pupils very small).</p>	+spinal fluid
<p>5b Second wife (A. O'B.); married at 28; heretofore healthy; one dead born child; left husband six years later, but did not marry again, and lived a secluded life with parents; soon became manager of father's business (large export commerce); seven years later symptoms of paresis.</p>		<p>Paresis (Depressive form; amnesia paretic speech; attacks of transient aphasia; K. J. ++).</p>	+spinal fluid

NO. NAME, OCCUPATION, AGE AND INCIDENTS OF MEDICAL LIFE	DIAGNOSIS	ONSET OF SYPHILITIC INFECTION	WASSERMANN TEST
6. F. D.; official of railroad; age 51; one legitimate and one illegitimate wife.	Paresis (Expansive; parietic speech; tremor; K. G. unequal and irregular pupils.)	denied	+spinal fluid
6a First wife (S. D.); legitimate; married at 20; heretofore in excellent health; two miscarriages; one child epileptic; one child healthy; began to show symptoms of tabes at 32.	Tabes (Loss of reflexes; ataxia; lancinating pain in limbs; Argyll Robertson pupils.)		
6b Second wife (mistress); (A. O'H.) a married woman; had three healthy children with her husband; heretofore healthy; after five years of double life she developed symptoms of tabes and the husband signs of cerebrospinal syphilis (with positive Wassermann of spinal fluid).	Tabes (Ataxia; loss of reflexes; unequal pupils).		+spinal fluid
7 Widow, E. R.; act. 35 (husband died at 38 following an apoplectic attack; had a chancre at 27, one year before marriage); she had sexual relations with two men; began to show symptoms of tabes (one year after husband's death).	Tabes (Ataxia, marked diminution of reflexes; Argyll Robertson of one pupil).		+spinal fluid
7a Man (S. Y., single), 40; bookkeeper, had relation with the woman, (No. 7), for 5 years; soon commenced to show symptoms of cerebral syphilis.	Cerebral syphilis. (Headache, poor memory; somnolence).	denied	+serum



NO. NAME, OCCUPATION, AGE AND INCIDENTS OF MEDICAL LIFE	DIAGNOSIS	ONSET OF SYPHILITIC INFECTION	WASSERMANN TEST
7b Man of 38 (C.S.); married; salesman; two healthy children, had relations with woman No. 7 for 8 years, when he commenced to show symptoms of tabes.	Tabes (Lancinating pains; ataxia reflexes obtained with difficulty and only occasionally; bladder—frequent retention; Argyll Robertson unilateral).	denied	+spinal fluid
S D. McC.; act. 42; bookbinder.	Taboparesis (Expansive form; loss of reflexes; double optic atrophy; ataxia; attacks of petit mal).	at 20	+serum and +spinal fluid
8a S. McC.; wife; married at 20; one miscarriage; two mentally defective children at 30; began to show evidences of paresis.	Paresis (Depressive form; K. G.; unequal pupils; parietic speech; tremor of tongue and fingers).		+spinal fluid
9 J. P.; act. 40; single, teacher.	Paresis (Depressive form; characteristic speech; tremor of hand and lips; K. G.; unequal pupils.	denied	+spinal fluid
9a Mistress (1st) of J. P.; act. 29; had relations with him for 6 years; never was married before; commenced to show signs of tabes at 29.	Tabes (Shooting pain in the legs; ataxia; K. J.; loss of Achilles' tendon reflex; Argyll Robertson of one eye).		+spinal fluid
9b Mistress (2nd) of J. P.; act. 31; relations with him for 8 years; first headache at 25.	Severe and persistent headache; some disturbance of micturition; K. G. markedly diminished.		+serum and +spinal fluid
9c Sister of J. P., act. 22; lived in the same house with him since infancy. (Parents left five healthy children; died in an accident; heretofore in good health.)	Severe headache; Argyll Robertson pupil of one eye.		+spinal fluid

NO. NAME, OCCUPATION, AGE AND INCIDENTS OF MEDICAL LIFE	DIAGNOSIS	ONSET OF SYPHILITIC INFECTION	WASSERMANN TEST
10 J. H.; act. 50; physician; married at 27.	Taboparesis (Expansive form; K. G. and Achilles lost; bladder disturbance; some ataxia).	at 32 from his mistress whose blood showed Wassermann.	+serum and +spinal fluid
10a M. H. wife; act. 48; married at 22; first signs of the affection at 38; two miscarriages and one son; latter born one year after marriage.	Tabes (Ataxia, sharp pain in legs; K. G. and Achilles lost; Argyll Robertson of both eyes.)		+serum
10b D. H.; son of J. H.; single; act. 23; bookkeeper; first signs of the affection at 22.	Persistent headache; marked diminution of reflexes, pupils react to light weakly.		+spinal fluid
11 W. J.; act. 39; merchant; married at 25; first signs of visual disturbance at 27.	Blindness with double optic atrophy; K. G. much diminished.	at 20	+serum and +spinal fluid
11a A. J.; wife; act. 33; married at 19; first signs of visual disorder at 30.	Blindness from double optic atrophy. Slight ataxia in gait.		+spinal fluid
12 W. K.; banker; act. 49; married twice; at 27 and 35; first evidence of disease at 38.	Paresis (Expansive form; irregular and small pupils; parietic speech; K. G.)	at 20	+serum and +spinal fluid
12a First wife, M. K.; married at 19; divorced after 5 years; no children; one miscarriage; first signs of disease at 28.	Tabes (Lost reflexes; bladder disorder; sharp pains in lower limbs.)		+spinal fluid
12b Second wife, A. K.; married at 32; no children; first signs of the disease at 40.	Paresis (Depressive; attacks of petit mal; K. G.; parietic speech; tremor of lips; pupils unequal.)		+spinal fluid

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## SYPHILIS OF THE NERVOUS SYSTEM IN CHILDREN

BY EDWARD LIVINGSTON HUNT, M.D., NEW YORK CITY

*Assistant Professor of Clinical Neurology, Columbia University, New York*

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I WANT to call your attention to some of the manifestations of syphilis of the nervous system in children, and to illustrate these remarks by a few cases. To make these statements clear it is necessary to consider in what respects congenital and acquired syphilis differ as, of course, most syphilis in children is congenital. The two conditions are far more similar than dissimilar. In the congenital type, the involvement of the human tissues is more general and more complex than in the acquired; more tissues are involved and the involvement itself is more complete and more complicated than in the acquired type. Apparently, fetal tissue displays a very poor resistance. The fact, therefore, that in congenital syphilis the infection is more rapid, more general, and more complex results in the nervous system becoming involved more frequently and earlier. One would expect practically the same train of clinical symptoms in the two types and as a matter of fact the clinical symptoms of involvement of the nervous system are quite similar. There do exist, however, certain variations and differences. I shall try to tell you of these in a few words.

In the *congenital* type, signs of involvement of the brain are more frequent than are those of involvement of the spinal cord. As a result, paralyses, mental symptoms, and optic atrophy are the usual symptoms of congenital syphilis, whereas ataxia, being of spinal origin, is comparatively rare. The reverse is probably true in the *acquired* type.

In the congenital type *occur* mental symptoms which result from maldevelopment or defects of the brain—a condition rarely present in the acquired. In the congenital type the nervous symptoms while they may be of almost any type, are far less apt to be of meningeal origin than is the case in the acquired form.

There is very little for me to say as regards the pathological changes

in congenital syphilis. They are practically the same as in the acquired type. I mean the same structures are affected and in the same way. However, in the congenital type one is more apt to find a combination of the various lesions, whereas in the acquired type they exist separately. In each type there occur arteritis, meningitis, and involvement of the brain, cord, and nerves. In the acquired type one can differentiate between these different types; in the congenital this is more difficult, if not impossible.

In the congenital type the clinical signs seem to point to a more general involvement than is the case in the acquired type.

Finally, the more carefully the congenital type of syphilis is studied the more convinced do we become that the nervous system is involved and involved at an early date.

In congenital syphilis there are certain stigmata which are frequent and sufficiently characteristic to warrant mention. These are Hutchinson teeth, saddle nose, striæ about the mouth, prominent veins, hydrocephalic head, and scaphoid scapulæ. Hutchinson teeth are not as common as has been taught. They are rarely seen in the adult because congenital syphilis rarely reaches the adult stage. A few teeth are more apt to be involved than many. I have at present under observation a case of congenital syphilis in which only one, an incisor, is peg-topped and crescentic, and I know of a second in which the two front teeth alone are of the Hutchinson type. The upper teeth are more apt to show the condition than the lower.

I have now a case under treatment which illustrates some of these points. He is a boy of twelve, who has an unusually large head, immobile pupils, a saddle nose, and two Hutchinson teeth. His reflexes are exaggerated. He has poor control over his sphincters. Mentally he is very childish and simple, and has never been able to take any schooling. For the past two or three years, he has developed convulsions. His blood had never been examined but upon admission to the hospital was shown to be four plus. The spinal fluid was also positive, the cell count slightly increased, and the gold-sol test revealed a luetic curve, that is a slight degree of irritation. This patient is evidently one of advanced syphilis. He has not responded to treatment. When all the data was collected, I suggested to the house physician that he make an examination of the mother's blood. It showed a strongly positive Wassermann reaction.

Mental defectiveness and deficiency are common in syphilitic children.

A great many instances of backward children, defectives, mild and severe imbecility, and even idiocy are the result of syphilis. The clinical signs in these cases vary greatly from restlessness, insomnia, and enuresis, through failure in school and inability to keep up with normal children, to marked childishness, defectiveness, and amentia. In the study of syphilitic children the examination of the spinal fluid is most important. The cerebrospinal fluid tests are four in number and familiar to most of us. There is the Wassermann reaction, the increased cell count, the excess of globulin, and most significant of all the changes from the normal curve as evidenced by the colloidal gold solution. In the well developed cases of juvenile tabes and paresis the reaction to the gold-sol test will show characteristic curves. In those other instances in which there are no signs of any definite but rather general indications of syphilitic involvement, the cerebrospinal fluid may at any early period give evidences of syphilitic irritation. It may vary from the normal even before physical signs appear. This test is the most delicate of all and often the curve will show only slight evidences of irritation rising to 1,  $1\frac{1}{2}$ , or 2, and in succeeding tubes revert back to normal. The more frequently the spinal fluid is examined and the more thoroughly syphilis is studied, the more evident becomes the fact that the involvement of the nervous system is an early feature of syphilis. This involvement is more general and appears at an earlier time in congenital than in acquired syphilis. Therefore, the lumbar puncture becomes an essential part of the examination of *every case of suspected syphilis*, of *every case where syphilis is hereditary*, and even of *every case characterized by nervousness, backwardness, and defectiveness*.

The blood Wassermann frequently shows changes. It may respond as often as does the cerebrospinal fluid but not always as early. Too much stress should not be placed upon a negative blood Wassermann. In fact in those cases in which syphilis in the ancestry is admitted and syphilis in the child is suspected, a negative blood Wassermann should weigh very little and not at all in those instances in which the spinal fluid shows positive returns.

The indications of an involvement of the nervous system in congenital syphilis afforded by a physical examination are well known.



They consist of changes in the reflexes, motor and sensory changes, abnormalities of gait, tremors, and so forth, in fact all the phenomena which a careful and systemic examination of the nervous system will bring out. It must always be remembered that the physical signs of syphilis of the nervous system are multitudinous and protean. Syphilis may simulate any condition.

An instance of nervous syphilis in children is the following: Henry W. was admitted to St. Luke's Hospital last March. He was just a year old. His mother stated that since his birth he had not been able to assimilate his food, that he had lost weight persistently, and was gradually, as she expressed it, going down hill.

He had never been able to sit up straight, and had never had control of either sphincter. At birth he was apparently normal, and a full term baby who nursed at the breast for nine months. There were no skin eruptions but he had had snuffles since birth. The physical examination showed—*rachitis* to an extreme degree, with a very square and somewhat enlarged head, *wide open fontanelles*, the *typical rosary on the chest*, a pot belly, and bow legs. *His pupils reacted sluggishly to light and accommodation, the eye movements were normal. Of the two teeth present both appeared normal. The x-ray* showed an involvement of the entire left lung. *Liver and spleen* were both enlarged. *The reflexes* were present. *There was a marked enlargement of the epiphyses* at both wrist and ankle and over the body there was a general lymphatic enlargement. *The laboratory reports* showed a blood count of 2,800,000, hemoglobin of only 36 per cent, 4 plus blood Wassermann, a spinal fluid with a negative Wassermann, 2 cells—100 per cent lymphocytes and a colloidal gold curve of 1222500000.

This child was given one dose of 0.15 gr. of neosalvarsan, and mercury hypodermically. He got progressively worse and regardless of all efforts in a very few days died.

*Juvenile paresis* is of all the various forms seen in syphilis of children the most frequent. It is very similar to the adult type. Convulsions which occur late in the adult paretic appear earlier in the juvenile. The average age at which the diagnosis of juvenile paresis may be made is twelve. Cases have been reported as early as six, seven, and three. The juvenile paretic is far more apt to have complications than is the adult, a fact probably due to the more general and complex pathologic involvement. In one case which I reported, several years ago, the patient showed a definite paretic curve at twelve while at the same time the Wassermann test was positive in two brothers, one sister, and the mother. In another, the Wassermann was positive in both the father and mother. The presence, therefore, of a case of juvenile paresis in a family should place upon the attending physi-

cian the duty of examining every member of the immediate family.

Another point of difference which I have noticed between paresis of the child and of the adult is the degree of emaciation. It is usual to find a gain of weight in the adult whereas the reverse is true in the child. The majority of juvenile paretics show a considerable degree of emaciation.

A fair instance of juvenile paresis is that of Josephine, aged 10 years. Patient was admitted with the mental symptoms of backwardness, nervousness, incoherence, and difficulty in talking. At six years of age she developed a transitory hemiplegia of the right side for four days. Recovery slow. Then she had a similar attack at nine years. Since this she has appeared simple-minded, slow, and incoherent in her speech, jabbers. Difficulty in controlling her sphincters since birth. Child was normal at birth, full term. No snuffles or skin lesions. Last two pregnancies have been abortions.

*Physical.*—Silly looking, and emaciated. Unequal, irregular pupils, no reaction to light and accommodation. Hutchinson teeth. Enlarged liver (2 cm. below ribs). No spleen enlargement. Reflexes absent. Ataxia, negative.

*Laboratory.*—Blood: red cells 4,800,000; hemoglobin 81 per cent; white blood cells 5,800—P. 62—L. 38. Spinal fluid: cells 5, L. 100 per cent, Wassermann 4 plus, colloidal gold 55454352510500. Blood Wassermann, 4 plus.

*Treatment.*—Two doses of salvarsan 3/10 gram.

*Course.*—Child had two attacks of petit mal during her stay in hospital with loss of consciousness. No cry or sleeping afterwards.

*Father's Wassermann*, 4 plus (blood) alcoholic antigen.

*Mother's Wassermann*, 1 plus (blood).

Here then is a typical case of juvenile paresis with both physical and mental signs, the syphilitic stigmata, the characteristic paretic curve in the spinal fluid, and convulsions. This child has been under my observation for over a year, has had several intravenous doses of salvarsan and so far as I can see shows no improvement over the condition of a year ago.

Juvenile tabes is more unusual than juvenile paresis. This, also, is probably to be accounted for by the more general and complex involvement so characteristic of the congenital type of syphilis. Those cases in which the spinal cord shows an involvement are far more apt to have a similar involvement of the brain. The average age of juvenile tabes is fifteen. Southard and Solomon reported one at twelve, and Lereboullet and Manyon at fifteen. Others have been cited in the twenties and early thirties.

It is a curious fact that pure spinal syphilis is almost unknown in

congenital syphilis. Nonne says he has never seen a case. This is in keeping with the rarity of juvenile tabes. The probable explanation is that the fetal brain tissue is far more susceptible to the specific virus than is that of the spinal cord.

Epileptic seizures are common in congenital syphilis. The condition should not be designated as epilepsy, but as a form of convulsion. We are far too apt to diagnose epilepsy, give bromides, and dismiss the case, forgetting that many instances of epilepsy in children are cases of congenital syphilis. In epilepsy, syphilis should always be thought of as a cause and every epileptic should have a cerebrospinal analysis.

It is often forgotten that diabetes insipidus is a characteristic symptom of congenital syphilis, the lesion being in the pituitary body.

A fair instance in which the involvement of the nervous system is beginning to be manifested is that of Edward D., age eight years, admitted May 11.

*History.*—Normal delivery and normal baby. No earmarks of lues at birth. Nursed 9 months, did well. Has always complained of blood in urine. Spells of unconsciousness came on about 5 years of age and became more frequent and severe as child grew older. Hands and feet became cyanotic and cold (attacks last only 2 hours). His mother brought him to O. P. D. where the blood was found 4 plus Wassermann. Family Wassermann records as follows: Father, blood Wassermann, 0; Mother, blood Wassermann, 4 plus; Brother, 13 years, Wassermann, 4 plus; 2 brothers, Wassermann, 0.

*Physical.*—Well-nourished boy. Pupils slightly irregular, react sluggishly. Teeth—erosion of enamel, poor condition (Hutchinson?). Enlarged tonsils. Reflexes present and equal.

*Laboratory.*—Blood—red cells 4,000,000—hemoglobin 59 per cent, white blood cells 6,900; P. 60, L. 40. Blood Wassermann, 4 plus. Spinal fluid, cells 1—L. 100 per cent, Wassermann negative, colloidal gold 11110500000.

*Treatment.*—Salvarsan 3/10 gram (2 doses). Intramuscular injections of mercury and mixed treatment by mouth.

*Course.*—Child had 2 attacks of cyanotic hands and feet lasting about 3 hours. Relieved by hot stupes and nitroglycerine and adrenalin.

Hydrocephalus is a frequent symptom. It may occur at birth, during early infancy, or even several years later. It is the result of an accumulation of fluid in the ventricles, and, when syphilitic in origin, is usually caused by an arteritis. In some instances it may be the result of a meningitis. The most frequent time for hydrocephalus to appear is in the first few months. It may be preceded or accompanied



by marked symptoms of irritability, insomnia, crying, and restlessness, or it may develop slowly without any symptom.

As the cranial nerves are so frequently involved in acquired syphilis and as we always associate cranial nerve paralysis with syphilis, it is not out of place to say a word regarding the cranial nerve involvement in the congenital types.

The most frequent cranial nerve to be affected in congenital syphilis is the eighth. This may be due to its extensive ramification and great susceptibility to toxemia. The involvement is not always very marked; it is however common to find minor changes. The pathological lesion is either a neuritis or an exudate around the nerve. Klauder states that the cranial nerves are involved in the following order of frequency, 8-2-3-4-5-6-7.

There are many cases of simple backwardness, of mental deficiency, and of pure nervousness in children, the fundamental cause of which is syphilis. Therefore, in all instances where nervous phenomena manifest themselves in children, suspect syphilis. In all cases of so-called nervous children a lumbar puncture is indicated, and, from this, the most important deduction is the gold-sol test.

The prognosis in congenital syphilis is bad; it is far worse than in acquired syphilis. This can be accounted for by the general and complex involvement, by the many cases of defective development and by the malformations of nervous tissue.

Finally, there occur certain types of mental defect in (children of syphilitic parents), who, however, show no obvious syphilitic lesions. Whether or not however these children may not later on develop either definite syphilitic lesions or respond to Wassermann tests in either blood or spinal fluid is still a question. Therefore, the physician cannot be relieved of responsibility in taking care of the offspring of syphilitics unless he frequently makes a Wassermann test on the blood and a gold-sol test on the spinal fluid.

The age at which syphilis may develop in children varies greatly. I have records of cases occurring at one, seven, eight, ten, twelve, fourteen and sixteen. The literature on the subject shows the same wide variations. Most authorities seem to agree that if any year can be named as the most usual it is the twelfth.

In the development of congenital syphilis certain factors with which we are not thoroughly familiar act as precipitating causes. One of

these is the presence of an infectious disease. The occurrence of either measles, influenza, or scarlet fever in a case of congenital syphilis, will very rapidly develop the symptoms and clinical signs of the underlying condition.

The Wassermann test on the blood is more reliable in congenital syphilis than it is in the acquired form. Holt says that it is positive in practically 100 per cent of untreated syphilitic infants. The same is true of the luetin test, which Noguchi says is true in 70 per cent and another observer in 93 per cent.

A case showing futility of treatment—Letitia M., age 7 years, admitted the 12th of March, 1920.

*History.*—Since birth, patient has had trouble with her bladder. Has always had to empty it very frequently and can pass only a small amount of urine at a time. Normal delivery. Normal baby, nursed for three months, gained slowly. Child, however, has been weak and delicate, has been much underweight and undeveloped. No mental symptoms. The urinary symptoms became worse. Cystitis developed and probably pyelitis. Now there is no control over the urinary sphincter and bowels are incontinent.

*Physical.*—Malnutrition and anemia. Pupils equal, regular, react to light and accommodation. Teeth—very poor, rotten, large cavities. Enlarged abdomen and spleen. Reflexes present, knee jerks 2 plus.

*Laboratory.*—Red blood cells 3,900,000, hemoglobin 59 per cent, white blood cells 18,000, P. 87, L. 13. Lumbar puncture—cells 3—L. 100 per cent. Wassermann negative, colloidal gold 1152325050000. Blood Wassermann 4 plus. Father's Wassermann, negative and negative spinal fluid. Mother's Wassermann, 4 plus.

*Treatment.*—Local measures for cystitis (irrigations). Neosalvarsan 0.15 grams (3 doses). Intramuscular injections b.i.d. of mercury.

*Course.*—Bladder and bowel control improving slowly, child's general condition same. Oct. 12, 1920, patient has had 14 intravenous doses of neosalvarsan 0.15 gr. bichloride hg. gr.  $\frac{1}{2}$  every week, no improvement.

One of the earliest cases of neurosyphilis is the following—A. C. was born at Sloane Maternity Hospital, and when brought to my notice was 15 weeks old. The baby was premature, labor having been induced at the eighth month. At birth he weighed 5 pounds, 8 ounces. When the child entered the hospital he had fissures about the mouth, snuffles, a pustular eruption on both legs and great asthenia. The mother said that he had never seemed well and had never nursed well. The blood Wassermann was four plus, responding to both antigens. The spinal fluid analysis showed 7 cells, of which 6 were lymphocytes, and one was a polynuclear. The butyric acid test was indeterminate

and the Wassermann negative. The colloidal gold curve, however, gave evidences of irritation and was reported as 1.5-1.5-1.5-1.5-1.0-0.5-0000.

A curious fact was that the laboratory reported the mother's blood Wassermann as negative but the spinal fluid Wassermann as 4 plus.

The conclusions which may be reached in this little study of syphilis of the nervous system in children are:

1. The condition is common.
2. The nervous system may be involved early.
3. A lumbar puncture may be of great help and should be a routine part of the examination of every nervous child.
4. Syphilis in children necessitates a blood and spinal fluid examination of the parents and vice versa.
5. Treatment is not very promising.
6. The stigmata are not necessary or even very frequent.



## TREATMENT OF SYPHILIS

REPORT OF A SERIES OF CASES TREATED AT CORNELL DISPENSARY,  
NEW YORK

BY SAMUEL FELDMAN, M.D., NEW YORK CITY

*From the Department of Dermatology, Cornell University Medical College.*

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IN my service within a period of about four years, from 1914 to March, 1918, 998 cases of syphilis came under observation. Of these 742 discontinued treatment before one course was completed and a blood test taken, and are of no value for statistical purposes; 256 remained long enough for further observation and the results will be tabulated later.

There were 56 cases of primary lues of the following types: 43 single genital chancres, 4 multiple chancres, 2 endourethral chancres, and 3 extragenital chancres.

In 53 cases, while the chancre was still present and unhealed, a rash appeared. Of these eruptions 28 were macules and only 9 were papules. As these eruptions appear with equal frequency in secondary lues, as will be shown, the greater frequency of the macular eruption in this group of cases conclusively proves that the latter type of eruption is the earlier to appear during the course of the disease. The lesions were as follows: 23 chancre and macules; 5 chancre, macules and mucous patch; 6 chancre and papules; 2 chancre and papulosquamous; 1 chancre and lenticular papules; 4 chancre and mucous patches; and 12 chancre and general adenopathy.

The balance of the secondary lues cases were either with healed chancre or presented no evidence of it having been present and its history was denied. A number of these cases can be accounted for by healed and overlooked chancres of the body cavities, such as the male urethra, the vagina, or the oral and nasal cavities. There was an even number, 70 cases each of macular and of papular eruptions. In 11 cases, 6 per cent, a history of chancre was denied.

35 macules	3 papulotubercular
4 macules and mucous patches	13 condylomata lata
1 macules and alopecia	16 mucous patches
1 macules and condyloma latum	3 tubercular
1 recurrent macules	2 palmar and plantar tubercles
18 maculopapular	1 vesicles and crusts
21 miliary and larger papules	1 vesicles and scaling
6 lenticular papules	1 bullæ on the feet on a copper-colored base
4 corymbiform	1 small pustular
3 circinate papules	3 aene syphilitica
1 gyrate patch made up of papules	6 rupia
1 papules resembling urticaria	5 vitiligo
1 papules resembling urticaria, with pigmentation	3 alopecia luetica
11 papulosquamous	3 angina
2 papulovesicular	12 adenopathy, less than one year duration
1 papulonecrotic	3 pigmentation
6 papulopustular	

We admitted 189 cases of tertiary lues during the above mentioned period. Of these 128 presented the following skin types:

6 discrete tertiary papules	1 tubercular, disseminated
3 circinate papules	11 tuberculo-serpiginous
5 tuberculo-serpiginous, ulcerations	2 gumma, pustular eruption
1 tuberculo-serpiginous, crusts	4 serpiginous gummata
1 tuberculo-serpiginous, gumma	13 leg ulcers
9 keratosis palmaris et plantaris	4 ulcers and scars on the body
2 psoriasiform patches	8 serpiginous ulcers
1 lichenified patch, copper colored papules on border	1 ulcer on heel of foot, resembling perforating ulcer
1 serpiginous area of alopecia with pigmentation	10 scars
33 gummata	7 scars with pigmentation
1 gumma, resembling keloid	4 pigmentation

There were 58 cases of tertiary lues involving the mucous membranes of the nose, mouth, pharynx and larynx, divided as follows:

12 mucous patches, older than one year	1 laryngeal ulcer
16 leucoplakia buccalis	1 tonsillar swelling
1 leucoplakia of eyelid	2 tonsillar ulcer
1 rhagades about the mouth	4 perforated palate
5 glossitis	5 perforated septum
1 fissure of the tongue	1 gumma of the nose
4 pharyngitis	2 laryngitis
2 pharyngeal ulcer	

Twenty-nine tertiary cases were those in which the structures of the eye and the ear were attacked.

4 ptosis	3 iridocyclitis
4 iritis	1 choroiditis
5 keratitis	3 chorioretinitis
2 keratoiritis	4 optic nerve atrophy
1 cyclitis	1 auditory deafness

There were 21 glandular cases as follows:

6 adenopathy	1 enlarged parotids
2 very marked general adenopathy	8 orchitis
1 cervical adenitis, resembling tuberculosis	1 thyroiditis
1 ulcerating inguinal adenitis	1 hepatitis, aoritis

In a comparatively small number of cases of tertiary lues the bony frame and the joints were attacked. The whole group consists of 16 cases.

3 arthritis	1 osteomyelitis
1 swelling of the elbow	2 exostoses
5 periostitis	1 ankylosis of the knee
2 osteochondritis	1 cervical caries

Finally, a group of patients, 37 in number, with vague and indefinite symptoms, usually subjective in character, in which a diagnosis was made only after a careful and complete routine examination. These cases were usually referred from other departments of the dispensary for treatment:

2 severe anemia	1 vertigo
4 nervousness	3 precordial pains
4 general weakness	1 lumbago
9 general pains	6 joint pains
7 cephalalgia	

We had 80 patients with cerebrospinal lues, most of whom had tabes.

15 early tabes	8 paresis
36 late tabes	6 cerebral lues (type not stated)
1 tabes, inflammation about posterior roots	2 spinal lues
2 tabes, circinate papules	1 epileptiform attacks
5 gastric crisis only	1 hemiplegia
1 girdle sensation only	1 aphasia
	1 amyotrophic lateral sclerosis



Of the 316 cases of latent lues, 31 denied any infection of lues. They suspected lues on account of the presence of the disease in some member of the immediate family or because of the history of repeated abortions. Other latent cases, again, came to have their blood tested on account of the need of obtaining food handler's certificates from the health department, otherwise they would have never had the slightest suspicion of ever having been infected. They were classified as follows: 19 luetic husband or wife; 5 luetic child; 7 abortions; 89 latent lues (less than one year); and 189 latent lues (more than one year).

There were only 10 cases of hereditary lues during the entire period of four years. Of these, 3 had typical Hutchinson teeth. Two others had a separation of the incisors, which is held by some observers to be another form of malformation of the teeth in hereditary lues.

Before 1914 and during the first few months of that year a course of treatment consisted of 10 mercury and 5 salvarsan injections. After each course a Wassermann test was made and if the latter was negative, the patient was ordered to return after a month for another test. As expected, a number of cases showed positive Wassermann again after one or more months of no treatment. Several cases returned to positive after a period of observation and blood testing of one year and more, even after as long a period as two years. The above experience showed the necessity of a change and at present the treatment is not discontinued after one course, even if the reaction becomes negative, but three and even more courses of treatment are given to the patient, unless the latter disappears of his own accord. Furthermore the course has been increased to 15 mercury and 5 salvarsan injections.

The dose of salvarsan administered until very recently was rather small, namely, 0.2 gram. It is now changed to 0.6 gram. The results obtained from the very small dose are rather encouraging. I regret that we did not treat enough cases as yet with the larger dose to be able to make any comparisons. In all we gave during the four years about 9100 mercury injections and more than 1700 salvarsan treatments.

We had only 20 reactions after salvarsan on our records. Most of them were mild reactions with the usual chill, fever and vomiting. Only two fairly severe reactions were observed, both in the same pa-

tient. In three instances the reactions were of a special nature. In one patient icterus developed several hours after treatment, in another one, herpes labialis, and in the last patient there developed a general urticarial eruption before he received the entire 50 c.c. of the solution. The small number of reactions is, of course, mainly accounted for by the small dose used. There was no difference noticed in the number or severity of reactions between the German and American preparations. If anything the records show fewer reactions from the latter drug than from the former. We now use exclusively the product of the dermatologic research laboratories of Philadelphia. I take the liberty of including the above statement because the preparation is not manufactured for private profit, but the whole income goes for the advancement of further research work in dermatology and the product must necessarily be reliable. When we first began to use the American preparation we experienced some difficulty; namely, in a proportionately large number of cases phlebitis developed with subsequent occlusion of the affected vein. This was, however, quickly remedied, when it was discovered that the fault was not in the preparation, but in the method of getting it in solution. It is a fact that practically all American arsphenamine preparations are rather difficult to dissolve and in order to facilitate the solution heating on a hot water-bath is recommended. Sometimes it may even be necessary to bring the liquid to the boiling point to make it dissolve properly. Heating a comparatively unstable arsenic preparation may cause breaking up of the chemical compound with liberation of free arsenic which may readily cause trouble. We obviate the necessity of heating the solution by throwing the arsphenamine into a perfectly dry and sterile flask and by shaking the contents vigorously until the drug becomes divided up into a very fine powder, after which it dissolves quite readily in luke warm water.\*

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\*Since the time this article was written, we have given about one thousand more arsphenamine treatments. All the arsphenamine was obtained from the Dermatological Research Laboratories of Philadelphia. With but a few exceptions, all patients received a full dose of 0.6 gm. of the preparation. Those that received less than the full dose, were either adults in poor health, or young children. One child about four and one-half years old with hereditary lues we gave 0.2 gm. arsphenamine in each injection. We only had one reaction in the entire series and that was in a woman suffering from advanced tabes and who was, at the time the treatment was given, in poor condition. Not one injection was followed by phlebitis. Referring to the causation of phlebitis in several of the first group of patients treated with the above mentioned preparation, the writer wishes to add the following. After having used the preparation for several months, we recorded that at first it was difficult to make the solution entirely clear by neutralization. There was always a little cloudiness, no matter how much sodium hydroxide was added. This undoubtedly was the cause of over-alkalization in several instances, resulting in phlebitis. In time, however, we found it quite

We had 11 mishaps from mercury injections. There were nine infiltrations, none of which went on to suppuration. One patient began to cough and expectorate blood immediately after a mercury injection and another one had chills and a bloody diarrhea several hours after.

Of the 19 patients with primary lues, two had only one course of treatment each. They both had positive Wassermann reactions on admission and both disappeared from further observation, one with a positive reaction and the other with a negative. The remaining 17 patients had each more than one course of treatment. Eight of these patients had negative reactions on admission and the diagnosis was made by positive spirochete findings under dark field illumination; 4 had positive reactions and on 5 patients no tests were made. Case VIII had a negative Wassermann on admission, but mucous patches developed in spite of four weeks of treatment with mercury and salvarsan and he disappeared from further observation with a plus 1 reaction after 3 courses of treatment. Case XIII was one of multiple chancres. He had a bad infiltration after one mercury injection, which, however, cleared up by itself.

Of the 9 patients who showed a negative reaction on admission, 4 became positive after treatment.

Two patients disappeared with a 4 plus reaction and 2 with a 1 plus.

Two disappeared after one negative test and one after being negative 2 months.

Two remained negative for one year and twenty-two months, respectively.

Of those having a positive Wassermann on admission:

Two remained 4 plus and one one plus.

One disappeared after one negative and one after being negative for 8 months.

One stayed negative two and one-half years.

This shows that the proportion of cures in the cases that received treatment before the blood became positive is not much greater than in those who had already had a systemic invasion. Whether the re-

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easy to completely clear the preparation with the alkaline solution. The results were entirely satisfactory. Although we hesitated for several months before we decided to use the Philadelphia product (for several months we treated our patients with mercury injections only, rather than take a chance with a new preparation), I now doubt whether any one of the men, associated with me at Cornell or in other institutions would change that product for even the well-tried and efficient German salvarsan.



sults might be better if the patients had received larger doses of salvarsan, the writer has no means of ascertaining at present.

In five instances no test was made.

Of the whole group of 19, six remained distinctly positive.

Four had a one plus reaction, which with a cholesterin reinforced antigen, as is being in use at Cornell, cannot be regarded as distinctly positive.

Three patients disappeared after the first negative reaction.

Three patients remained negative for 2 months, 4 months and 8 months, respectively.

Three stayed negative from 1 to 2½ years.

Proportion of cases apparently unaffected 31½ per cent, apparently cured 16, the balance, 52½ per cent, disappeared before a definite result could be obtained.

There were 18 cases of early secondary lues in which the chancre was still unhealed. The duration from the time of infection was from 3 weeks to 3 months. Twelve cases were positive, 2 were negative and in 4 the test was not made. Fifteen patients had macular eruptions, one a maculopapular, 1 a papular and 1 a varioliform. In case No. 18 condyloma and interstitial glossitis developed 10 weeks after treatment was begun. He received 29 mercury and 4 salvarsan injections and he disappeared from the clinic with a plus 4 reaction. Case No. 23 had a fairly severe reaction after 0.2 gram of salvarsan.

Eight cases remained distinctly positive after several courses of treatment. The last Wassermann tests made on these patients ranged from plus 2 to plus 4.

One disappeared with a plus 1 reaction.

Two disappeared after the first negative blood test.

One patient remained negative for 10 months and then disappeared from further observation.

Six stayed negative for periods of from one year to 26 months. The percentage of apparent cures being 33⅓.

The balance of the group of early secondary cases, 40 in number, were mostly older cases with healed chancre or without a history of it. The duration from the time of infection was from 1 to 9 months. In one case there developed an iridocystitis 3 weeks after treatment was started, but it cleared up rather rapidly, the reaction became negative and remained so for one year, when we lost track of him. In one case

of vitiligo on the back of the neck of a colored woman, circinate papules developed later about the mouth. One case was that of a pregnant woman in the sixth month and although her own blood did not become negative before she passed out of our control, she gave birth to an apparently normal child three months after she first came for treatment. A Wassermann test, made on the baby, proved negative.

In the above group there were 15 patients with papular eruptions, 8 with macular and 4 with pustular, the rest were adenopathies, mucous patches, etc. While the interval between the chancre and the appearance of the secondaries averaged 7 weeks in the first group of patients with secondary lesions, this group averaged  $3\frac{1}{2}$  months. Also while the proportion of macules to papules in the first group is 15 to 1, in this later group the papules predominate in the proportion of 15 papules to 8 macules again proving conclusively that the macular eruptions are those to appear at an earlier date after the initial lesion than the papular lesions.

The general supposition that the papular lesions indicate a more virulent infection is not borne out by our findings. From the patients with papular eruptions 10 remained positive and 10 became negative (50 per cent) the average length of the negative Wassermann being about 14 months, while in the patients with papular eruptions only 6 remained positive and 10 became negative (62.5 per cent) with an average duration of the negative Wassermann of  $11\frac{1}{2}$  months. The results seem still more peculiar when we consider the patients with pustular eruptions, accepted as the most virulent type of secondary infections. All the 5 patients with the above named lesions became negative, the average time the Wassermann remained so was 15 months.

To complete the group of secondaries 4 patients with late secondary eruptions must be added. The time of the appearance of the eruption in these patients was from 18 months to 2 years. Case 73 came with a condylomata 20 months after having had a chancre. His Wassermann reaction was negative on admission, but became positive after one course of treatment and shortly after he disappeared from the clinic. Of the 4 patients, 3 remained positive and one became negative after 28 mercury and 15 salvarsan injections. His blood remained negative for 1 year and then it became plus 1 again.

Of the whole group of patients with secondary lesions, 62 in all, 22 remained distinctly positive, 35.5 per cent; 7 gave indefinite reactions, 11 per cent; 12 became negative and they disappeared after the first negative reaction, 19 per cent; 4 patients had negative reactions for periods of from 4 months to 1 year when their reactions became positive again; 17 remained negative for periods of from 10 months to 3 years and 10 months, 29 per cent.

It has been, and still is, argued by some eminent syphilologists that patients with a positive Wassermann and with no lesions should not be treated. The basis for their belief is the assertion that once infected with syphilis, a patient carries it with him to his grave. I have not followed a single case from the date of infection of syphilis to his dying day and I have good reasons to doubt whether anybody has. I observed, however, several cases of latent lues, who had a plus four reaction when we started to treat them and who became negative and remained so for as long a period as four years. That I have not many more to report may be accounted for by the fact that dispensary patients shift very often and it is impossible to follow up the greater number of them. The next argument advanced against treating latent cases is that sometimes patients, who come for treatment with a negative blood reaction, become positive after treatment. In other words, treatment may light up an active infection in a dormant case. The experience we had at Cornell is that not a single case was harmed by antiluetic treatment. Furthermore, by far the greatest number of cases with negative Wassermanns that come for treatment are very old tertiaries with active lesions and cases of cerebrospinal lues. There is, of course, no disagreement as to the necessity of treating those cases. On this question the two extremes meet. For the next argument for not treating latent cases with positive Wassermann reactions is that those cases are actually cured and the presence of the positive reaction is accounted for by the theory that once the syphilitic virus invades the system, it alters the tissues so that the positive Wassermann persists indefinitely after a cure is effected. If that be so, why do patients develop severe tertiary lesions after latent periods of as long as twenty or thirty years? Then again every patient with active lesions will become latent after a shorter or longer period of treatment, the Wassermann reaction is bound to remain positive for a much longer period. Can anybody decide when treatment should be



discontinued? The only answer that can be given is that we must strive to obtain a negative reaction.

We treated altogether 77 cases of latent lues, 10 of which were early cases. None of them dated more than one year from the time of infection, the earliest case being 5 weeks. Out of the 10 cases, 4 remained positive, one had plus 1 reaction and 5 became negative. Three out of the 5 cases disappeared after the first negative test, one after being negative 6 months and one remained so for one year.

The rest of the latent cases can for the purpose of classification, be divided into two groups. One group of 18 cases of latent infections, the duration of which is unknown. Thirteen of these cases suspected the presence of lues on account of the presence of the disease in the husband or the wife, because of giving birth to a syphilitic child or because of miscarriages. The other 5 cases had their blood tested for the purpose of obtaining food handler's cards. Numbers 86 and 98 were both pregnant when they first came for treatment. They each gave birth to an apparently normal child. No. 94 began treatment 4 months after having given birth to a syphilitic child. Her Wassermann reaction became negative and remained so for 1 year, when she discontinued attendance at the clinic. No. 93 had a +3 Wassermann 6 months after childbirth with a syphilitic child. She became negative after the first course of treatment, +2 again after the fourth, then negative again. She remained so for two years under observation and then became +2 once more.

Eight cases remained distinctly positive, 4 cases with +4, 2 with +3 and 2 with +2.

One remained +1.

Nine became negative; 3 disappeared after the first test, 1 after remaining negative 6 months and 1 after 10 months.

Four remained negative for periods of from 1 year to 16 months.

Fifty per cent of this group gave negative reactions.

The other and larger group consisted of 49 patients, mostly very old cases, some of them of as long as thirty years' standing. Twenty-two of this group had only one course of treatment, and 27 were treated long enough to be of value in estimating the results. Case No. 117 was negative on admission and became strongly positive after treatment. Case No. 122 became negative after the first course, remained so for 8 months, and then became +4. Case No. 123 was negative for

one year after treatment, then became +4. Case No. 110 was under treatment when he came to the clinic with a negative Wassermann. His blood gave a positive reaction after the first course of treatment. It, however, cleared up after further treatment and it remained negative for 28 months.

Thirty cases remained distinctly positive, 19 with +4, 8 with +3, 3 with +2.

Four indeterminate reactions, 3 had +1 and 1  $\pm$ .

Fifteen became negative, 3 of these disappeared after the first test and 5 stayed negative from 3 to 8 months. One became positive after 8 months.

Seven remained negative from 1 to 3 years. One became positive again after 1 year.

Table I shows the result of treatment of all the 77 latent cases combined.

TABLE I

THOSE THAT HAD ONE COURSE				MORE THAN ONE COURSE		
REACTION	NO. OF CASES	TOTAL	%	NO. OF CASES	TOTAL	%
+4	14			10		
+3	3			9		
+2	3	pos. = 20	57	2	pos. = 21	50
+1	4			1		
$\pm$	1	indef. = 5	14	-	indef. = 1	2 $\frac{1}{3}$
0 once and disappeared	5			5		
0 6 months or less	-			6		
0 7 months to 1 yr.	4			2		
0 13 months to 1 $\frac{1}{2}$ yr.	-			3		
0 19 months to 2 yr.	1			2		
0 25 months to 2 $\frac{1}{2}$ yr.	-			1		
0 3 years	-	neg. = 10	29	1	neg. = 20	47 $\frac{2}{3}$
Became positive after being negative.		2	20		1	5

Even in the patients with active tertiary lesions, the results, in obtaining a negative Wassermann reaction, cannot be regarded as discouraging, except that the negative result in these cases was obtained after a much longer period of treatment (see appended table). There were altogether 61 patients in this group, 2 of which were early ter-

tiaries. One had a gumma of the thigh which developed 7 months after his initial lesion. His blood became negative after four salvarsans and about 40 mercury injections. It remained so for 4 months when we lost track of him. The other case, 1 of keratosis palmaris remained +4 after about the same amount of treatment. The rest were mostly old cases, some of them had the disease for 25 years. No. 135 developed carcinoma on top of an old gumma of the penis. No. 151 had a keratosis palmaris for a number of years, and although the patient received about 60 mercury injections, the lesions remained unchanged. The latter, however, cleared up after two arsphenamine injections. No. 163 had a positive reaction, both of his blood and his cerebrospinal fluid, although he had no symptoms of tabes. Both the blood and cerebrospinal fluid became negative after intravenous salvarsan and mercury injections. No. 164 is a case of syphilitic goiter with exophthalmos and cardiac and nervous symptoms. The circumference of the neck was, on admission,  $14\frac{1}{2}$  inches. The patient was too sick to take vigorous antisymphilitic treatment and she was treated with mixed treatment and with only an occasional mercury injection. The neck measurements were reduced to  $13\frac{1}{4}$  inches and the pulse from 140 to 90.

TABLE II

SUMMARY OF THE RESULTS OF TREATING THE 59 OLD TERTIARY LUES PATIENTS

CASES THAT RECEIVED ONE COURSE ONLY				MORE THAN ONE COURSE		
REACTION	NO. OF CASES	TOTAL	%	NO. OF CASES	TOTAL	%
+4	9			12		
+3	3			8		
+2	1	pos. = 13	65	3	pos. = 23	49
+1	1			3		
±	1	indef. = 2	10	-	indef. = 3	8
0 once and disappeared	3			6		
0 7 mo. to 1 yr.	2			4		
0 13 mo. to $1\frac{1}{2}$ yr.	-			2		
0 2 yr.	-	neg. = 5	25	1	neg. = 13	43
Became Positive after being negative		1	20		1	8

In addition to the patients with tertiary lues, mentioned above, we treated 9 with lesions involving the special sense organs of sight and



hearing. Of these 2 patients with optic nerve atrophy received only one course of treatment each and were not improved clinically, when they disappeared. Out of two patients with chorioretinitis, one had his vision slightly improved, while the other showed no perceptible change after treatment. In one patient with iridocyclitis the symptoms cleared up entirely, his blood became negative after 10 salvarsan and 20 mercury injections and it remained so for one year. Two patients with third nerve paralysis and 1 with keratitis were clinically cured although their blood remained positive. On the other hand a case of auditory deafness clinically showed no improvement, while his blood became negative and remained so for 11 months.

We had under observation only two cases of peripheral neuritis. Both were clinically cured. One disappeared after the first course of treatment with a plus 4 reaction, the other became negative and remained so for one year.

The final group of cases of acquired syphilis consists of 20 patients with cerebrospinal lues. Of these 6 cases had only one course of treatment, the other 14 had two or more courses. Five of the above mentioned six patients remained positive and clinically were not improved; only one became negative and was clinically improved. In the other 14 cases the clinical results were remarkably good. Not a single patient of this group had intraspinal injections, yet in 4 patients the symptoms have entirely disappeared. And the rest of the group except case No. 195, showed marked improvement. Five patients had early tabes, in three of them the symptoms disappeared completely, while in two the symptoms have improved greatly. Case No. 184 was referred to us from Prof. Dana's department. He was then suffering from epileptiform attacks, which came on about twice a week. He had only one attack after he received the first salvarsan injection and not a single recurrence during the 10 months of treatment and observation. Case No. 186 was brought over from Bellevue Hospital, in which institution she came right after a very severe attack of gastric crisis. She had a well-developed ataxia together with her general weakness after the gastric attacks, so that she could not shift for herself, but had to be supported by a nurse. The third visit to the clinic she came herself without any support. At present all her tabetic symptoms have disappeared. Her Wassermann reaction has been negative for the past 4 months. Considering the results ob-

tained from treating the cerebral lues cases with mercury and intravenous salvarsan injections, we never felt that our patients were the losers by not being subjected to the very severe ordeal of intraspinal salvarsan injections.\*

Table III summarizes the clinical results and the Wassermann reactions obtained in the 20 cerebrospinal lues cases.

TABLE III

CASES WHICH HAD ONLY ONE COURSE			MORE THAN ONE COURSE	
RESULT		%	RESULT	%
Cured	0	0	4	28.6
Improved	1	16.5	8	57.2
Unimproved	5	83.5	2	14.2
Wassermann positive	5	83.5	9	64.2
Wassermann negative	1	16.5	5	35.8

TABLE IV

THE 57 ONE COURSE CASES					THE WHOLE GROUP OF 156 CASES			
	NEG.	IND.	POS.	TOTAL	AFTER 1 COURSE			
	NEG.	IND.	POS.	TOTAL	NEG.	IND.	POS.	TOTAL
Primary	1	1	-	2	7	3	9	19
Secondary	1	-	2	3	23	13	23	59
Early latent	1	1	1	3	5	1	4	10
Old latent	1	3	18	22	19	8	39	66
Tertiary	3	2	13	18	18	4	37	59
Eye, ear	1	-	1	2	4	-	13	17
Per. neurit.	-	-	-	-	-	-	2	2
Cerebrospinal	1	-	4	5	5	3	12	20
Hereditary	-	-	2	2	-	-	4	4
Total	9	7	41	57	81	32	143	256
Per cent	16	12	72		31.5	12.5	56	

Four patients suffering from hereditary lues complete the list of patients that were under treatment for a considerable length of time. One was in the latent stage. Lues was suspected after the death of the child's father from active lues. This was the only case in which we managed to obtain a negative Wassermann reaction after three courses

\*At this point the writer is unable to refrain from adding an experience from his private practice. A patient with a plus 4 Wassermann reaction came for treatment after his wife gave birth to a syphilitic child. He had no clinical symptoms whatever. After 2 years of continuous treatment with salvarsan and mercury, he suddenly developed symptoms of paresis. In spite of the fact that salvarsan treatment was pushed to the limit, (0.6 every 4 days for six doses) he went from bad to worse. After about a month, he became so ataxic, that he is at present unable to shift for himself.

TABLE V

	AFTER 2 COURSES			3 COURSES			4 COURSES			5 COURSES		
	NEG.	IND.	POS. TOT.	NEG.	IND.	POS. TOT.	NEG.	IND.	POS. TOT.	NEG.	IND.	POS. TOT.
Primary	3	2	6 11	-	1	1 2	1	-	1 2	-	-	1 1
Secondary	16	6	16 38	10	5	7 22	6	1	3 10	1	-	2 3
Latent early	3	-	- 3	-	1	1 2	1	-	- 1	1	-	- 1
Latent old	11	6	16 33	14	1	1 26	4	1	8 13	3	1	2 6
Tertiary	6	6	19 31	6	1	7 24	4	1	10 15	4	1	5 10
Eye, ear	1	1	3 5	-	-	1 1	-	-	-	-	-	-
Per. neurit.	-	1	- 1	1	-	- 1	-	-	1 1	-	-	-
Cerebrospinal	16	3	5 14	2	-	2 4	-	-	-	-	-	-
Hereditary	-	-	2 2	1	-	- 1	-	-	-	-	-	-
Total	46	25	67 138	34	9	40 83	16	3	23 42	9	2	10 21
Per cent	33	18	49	41	11	48	38	7	55	43	9.5	47.5



of treatment. The other 3 patients, 2 with eye symptoms and one with periostitis of the tibia were clinically cured but their Wassermann reaction remained positive.

Table IV shows the result of treating the whole group of 57 cases which had 1 course of treatment only and then the whole group combined.

#### SUMMARY AND CONCLUSION

1. Salvarsan will clear up symptoms much more rapidly, than mercury.

2. Comparatively good results can be obtained from small doses of salvarsan and if for any reason, the patient's ability to tolerate large doses of salvarsan is doubted, the physician should not hesitate to use small doses.

3. Heating a salvarsan mixture is not advisable; it may give trouble.

4. In primary lues the result obtained by treating the patient before his blood becomes positive is somewhat, though not much, better than when treatment is instituted when there is already a systemic invasion.

5. The chances for obtaining a negative Wassermann reaction in cases of latent lues, even in very old cases, is very good and hence they should be treated.

6. The symptoms in tertiary lues will always clear up after treatment with mercury and especially salvarsan. Comparatively good results can even be had in obtaining a negative blood reaction, provided treatment is continued for a comparatively long time.

7. All early cerebrospinal cases are cured and a proportionately large number of old cases are favorably influenced by ordinary intravenous salvarsan and intramuscular mercury injections. The advantage claimed for intraspinal treatment does not seem to compensate for its disadvantage. An exception to the above statement is illustrated in the footnote on page 281.

8. A negative Wassermann reaction obtained after a single course of a few months of treatment does not indicate that a cure has been effected. A comparatively large proportion of patients returned to the positive Wassermann after a period of one year of abstaining from treatment and in one instance after two years. Treatment should be kept up at least one year after the first negative result and if the Wassermann is still negative at that time, treatment may be discontinued and the patient watched.

# A STUDY OF THE WASSERMANN REACTION IN A LARGE GROUP OF SUPPOSEDLY NONSYPHILITIC INDIVIDUALS, INCLUDING LARGE GROUPS OF DIABETICS AND NEPHRITICS

BY JOHN R. WILLIAMS, ROCHESTER, N. Y.

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VERY few studies of the Wassermann reaction in nonsyphilitic individuals have been published; except for the group studied by Stokes at the Mayo Clinic and Solomon's\* study of 3000 hospital admissions, none have come to my notice. That is to say, much of the information as to the prevalence of syphilis in the public at large is based upon the frequency with which positive Wassermans are found in clinics where the study and treatment of syphilis is a special consideration. Such figures are obviously misleading. My own practice and clinic, dealing chiefly with the average American middle class, is confined to internal medicine and the routine examination of normal individuals. I am rarely consulted because of known syphilitic lesions. For some time I have made a routine practice of having a Wassermann test done upon each individual whom I have examined. More than 65 per cent of these tests were made in the laboratory of the State Department of Health at Albany. The others were made in the laboratories of the Hahnemann Hospital, Rochester, N. Y., using for the most part the antigens as well as the methods of the State Laboratory. Doubtful and positive tests of each laboratory were as a rule confirmed by control tests in the other laboratory. The general findings in this study are summarized in the following tabulations.

Number of patients examined.....	912
Number of tests made.....	1040
Number of tests repeated.....	128
Number of cases showing 4 + Wassermann tests.....	33
Number of cases showing 3 + Wassermann tests.....	7

\*Solomon, H. C.: Jour. Am. Med. Assn., lxxiv, 788. Study of tests performed by two laboratories in 3,000 successive hospital admissions.

Number of normal individuals examined.....	97
Number of normal individuals showing negative Wassermanns.....	91
Number of normal individuals showing too anticomplementary Wassermanns	2
Number of normal individuals showing doubtful Wassermanns.....	4
Number of normal individuals showing positive Wassermanns.....	0

In the foregoing table, it will be observed that 40 individuals showed either a three- or four-plus reaction which for the purposes of this paper is assumed to be a positive reaction. In this group of 40 cases, 93 tests were made as follows:

33 cases	gave	46 four plus reactions
7 “	“	11 three plus “
6 “	“	8 two plus “
4 “	“	4 one plus “
10 “	“	15 negative “
3 “	“	5 doubtful “
2 “	“	4 too anticomplementary reactions.

On 24 of these cases, were found either by clinical or postmortem examination demonstrable evidences of syphilis. In 16 cases, such evidence is lacking, unless the clinical syndrome, diabetes mellitus, be accepted as evidence of syphilis.

The relation of syphilis to diabetes is both interesting and important. In my clinic, we have had the opportunity of studying a large number of diabetics with reference to syphilis.

Number of diabetic cases examined.....	337
Number of tests made.....	407
Number of tests repeated.....	70
Number of cases showing positive Wassermann reactions.....	16
Number of tests made on these 16 cases.....	45
Number of tests made showing positive reactions.....	22

It will be observed in the above table that sixteen proved cases of diabetes, at some time during their study, gave either a three or four plus Wassermann reaction, as well as negative and doubtful tests. The data with reference to the tests is further analyzed in the following table:

16 cases	gave	22 positive reactions
3 of the 16 cases	gave	5 two or one plus reactions
7 “ “ 16 “	“	13 negative reactions
2 “ “ 16 “	“	4 too anticomplementary reactions
1 case	gave	a doubtful reaction



In none of the foregoing cases was specific treatment for syphilis given.

It was observed that these discordant results were obtained chiefly in young diabetics who were suffering gravely from the malnutrition occasioned by the disease and in whom there was evident lipoidal disturbance. As the nutrition of these cases was improved by proper dietetic measures, there was a coincidental improvement in the Wassermann test. Thus, in each instance where a positive Wassermann test was obtained, the diabetes was very severe.

CASE NO.	SEX	AGE	REACTIONS
1521	M	11	4+, T.A., 4+, Neg., T.A., T.A., Neg.
2773	F	12	2+, 4+, Neg., 2+, 4+, T.A.
2765	F	12	3+, 1+, Neg., Neg.
2362	M	16	4+, Neg., Neg.
2253	F	21	4+, 2+, 1+, 4+, Neg., Neg., Neg.
2972	F	35	Doubtful, 3+, Doubtful, Doubtful.
3053	F	4	4+, Neg.

In the light of the information at hand, it is difficult to explain why these cases should at one time show a marked and definite positive Wassermann reaction and at another time give normal tests. In no other group of cases were these variable findings observed. There are a number of conjectural explanations. It is possible that the technic of the laboratories performing the tests was at fault. If this be true, then the complement-fixation work of the majority of best known laboratories in this country may be similarly questioned. It may be that these patients have syphilis, as has been intimated by one of the leading pathologists of this country. If this be true, the inconstant positive Wassermann reactions which were observed in the absence of any specific treatment is most anomalous and does not conform to the usual experience with the Wassermann reaction in the presence of syphilis, namely, that when syphilis is evident and the reaction is positive, it remains positive until altered by specific treatment.

The more plausible explanation is the one which has already been suggested. It would seem that there is a relationship between the nutritional state of these individuals and the variations in the Wassermann reaction. It was observed that the positive and partial reactions occurred when the patients for a long time had been on

diets far below the point of minimal basal metabolism, and were suffering severely from imperfect nutrition.

It is a well-known fact that in states of low nutrition and starvation, the body frequently mobilizes large amounts of fats and lipoids. Furthermore it is probable that the body lipoids enter into the mechanism of the Wassermann test. However, the clinical study of the body lipoids is still in its infancy, methods being neither comprehensive nor very exact. Using Bloor's cholesterol method, a number of observations were made on these cases, the results of which are shown in the following statement. The normal blood cholesterol is rarely over 200 mg. per 100 c.c. of blood.

Case 1521. Male, age 11 years. Severe diabetes.

	WASSER- MANN	CHOLES- TEROL	DIET	PHYSICAL CONDITION
On admission	4+	498 mg.	1000 calories	Very poor
After 1 month	4+	408 "	1100 "	Improved
After 12 months	Neg.	350 "	1200 "	Unchanged
After 24 months	Neg.		1200 "	Unchanged

Case 2773. Female, age 12 years. Severe diabetes.

	WASSER- MANN	CHOLES- TEROL	DIET	PHYSICAL CONDITION
On admission	4+	237 mg.	600 calories	Acute
After 1 month	Neg.		1200 "	Improved
After 3 months	4+	234 "	1300 "	"

Case 2765. Female, age 12 years. Severe diabetes.

	WASSER- MANN	CHOLES- TEROL	DIET	PHYSICAL CONDITION
On admission	3+	237mg.	400 calories	Poor
After 1 month	Neg.	288 "	1500 "	Fair
After 3 months	Neg.			Good

Case 2253. Female, age 23 years. Severe diabetes.

	WASSER- MANN	CHOLES- TEROL	DIET	PHYSICAL CONDITION
On admission	4+	227mg.	500 calories	Very poor
After 1 month	2+			" "
" 3 "	Doubtful	335 "	1400 "	Improved
" 12 "	4+	307 "	600 "	Poor
" 13 "	Neg.	425 "	425 "	"
" 14 "	Neg.	530 "	1200 "	"

It is not urged in this study that the variation in body lipoids is a factor which produces the discordant Wassermann tests. The facts are briefly: patients suffering from the malnutrition of severe diabetes frequently exhibit marked increase in blood lipoids, the cholesterol particularly being higher than normal. These patients show at various times positive and negative Wassermann tests. In none of them was evidence found pointing to syphilis other than that afforded by the complement-fixation test. No spinal fluid examinations were made in this group. The wisdom of administering antisypilitic medicines to patients severely ill with diabetes on such variable evidence as the Wassermann test is questionable. This problem is worthy of further study.

In a series of 38 individuals, chiefly diabetics, the reaction "too anticomplementary" was obtained. There were 48 such tests. In practically all of these cases, the cholesterol content of the blood was higher than normal, ranging from 250 to 500 mg. per 100 c.c. of blood.

Eleven individuals were studied who gave negative blood Wassermans who showed either clinical or postmortem evidence of syphilis. One case gave a three plus reaction, yet a most searching test at postmortem of blood vessels, testes, and other organs revealed no histological evidence of the disease.

A group of cases of nephritis were examined with the following results:

Number of cases examined.....	110
Number of tests made.....	124
Number of tests repeated.....	14
Number of cases showing positive reactions.....	1

A group of miscellaneous medical cases afflicted chiefly with blood, blood vessel, lymph gland disease, and simple infections, were also studied as follows:

Number of cases examined.....	368
Number of tests made.....	412
Number of cases showing negative reactions.....	277
Number of cases showing positive reactions.....	23
Number of cases showing too anticomplementary reactions....	8
Number of cases showing partial or doubtful reactions.....	47



## CONCLUSIONS

1. A group of 912 individuals representing chiefly the great American middle class population were examined clinically and by the Wassermann test with reference to syphilis. None of these individuals were known or supposed to have syphilis. Many of them were persons in good health, a large group were afflicted with diabetes, another large group with nephritis, while the remainder were ill with miscellaneous medical complaints.

2. Approximately 4.4 per cent of these 912 cases showed a positive Wassermann.

3. In a group of 337 diabetics, positive Wassermanns were obtained in 16 individuals or approximately 4.8 per cent after one or more tests of each case. No specific treatment for syphilis was given these 16 cases, nevertheless seven of them gave 13 negative reactions and three others gave doubtful reactions. The bloods of these cases all had an increased lipid content.

4. The Wassermann reaction in some cases of diabetes exhibits most remarkable variation, being strongly positive at times and either negative or faintly positive at others. These variations may be due to errors in laboratory technic or to physical chemical changes in the body of the diabetic. In either event, they suggest that great caution should be exercised in the interpretation of the results.

5. In 38 individuals, chiefly diabetics, whose sera were too anti-complementary, an increase in blood cholesterol was commonly noted.

6. In a group of 110 nephritics, only one positive Wassermann reaction was obtained.

7. In a group of 369 miscellaneous medical cases, there were 23 positive reactors, or approximately 6.2 per cent.

8. Approximately 2 per cent of the cases studied either had clinical or postmortem evidence of syphilis not revealed by the Wassermann test.

9. A negative Wassermann reaction in the face of suggestive physical findings should be confirmed by repeated tests. Likewise a positive Wassermann reaction in the face of negative clinical, history, and physical findings should be confirmed by further clinical laboratory investigations before the institution of drastic syphilitic treatment.

# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XVIII\*

## THE INFLUENCE OF THE ORDER OF MIXING SERUM, ANTIGEN AND COMPLEMENT AND TOTAL VOLUME UPON COMPLEMENT- FIXATION REACTIONS IN SYPHILIS

BY JOHN A. KOLMER, M.D., PHILADELPHIA, PA.

*From the Dermatological Research Laboratories of Philadelphia*

(Received for publication, November 30, 1920.)

APPARENTLY little or no attention has been given by serologists to the possible influence upon complement-fixation reactions in syphilis of the order in which patient's serum, antigen and complement are brought together in setting up the tests; probably the majority of workers place antigen first, followed immediately by serum, complement and saline solution.

The subject, however, would appear to possess some practical importance for the following reasons:

(a) If antigen and complement are first mixed and allowed to stand for some time before the addition of serum, it is possible that more of the complement will be absorbed or fixed by the antigen alone than occurs when antigen, complement, and serum are mixed in succession.

(b) If serum and complement are first mixed and allowed to stand for some time before the addition of antigen, it is possible that more of the complement will be absorbed or fixed by the serum alone than occurs when serum, complement, and antigen are mixed in rapid succession.

(c) If syphilitic serum and antigen are first mixed and allowed to stand for some time before the addition of complement, it is possible that the resulting precipitate will absorb or fix more or less complement than occurs when serum, antigen and complement are mixed in succession.

Likewise the total volume of the mixtures for complement fixation

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

tests has not received much discussion; Wassermann and his associates originally advocated a total volume of 5 c.c. and most serologists have followed this plan or adopted smaller amounts for the sake of economy, such as 2.5 c.c., 1.25 c.c. or 0.5 c.c. The subject is of some practical importance, inasmuch as the activity of complement depends in some degree on its concentration as well as upon the total amount present.

#### PURPOSES OF INVESTIGATION

The purposes of this investigation were to study these subjects from the standpoint of influence upon complement fixation as follows:

1. To determine the possible influence of the order of mixing serum, antigen, and complement upon complement fixation in syphilis.
2. To study the influence of total volume upon complement fixation in syphilis.

### Part 1

#### THE INFLUENCE OF THE ORDER OF MIXING SERUM, ANTIGEN, AND COMPLEMENT.

When complement-fixation tests are set up by first placing the antigen and complement in test tubes, followed one-half hour or longer by the serum, more of the complement is absorbed in a nonspecific manner by the antigen than when the three substances are mixed in succession; likewise if the patient's serum and complement are first mixed and allowed to stand for half an hour or longer at laboratory temperature (20°—22° C.) more complement is absorbed by the serum alone in a nonspecific manner than occurs when all three substances are mixed in succession.

These facts have been established by a series of experiments, the results of three being given in Tables I, II and III as examples.

Table I shows that when diluted complement is allowed to stand at 22° C. the unit of hemolytic activity remains quite constant for about two hours; however, when this diluted complement is mixed with the antigen and allowed to stand, the unit of hemolytic activity is sharply reduced within half an hour. These results were ascribed to the anticomplementary activity of the antigen, that is, the absorption of a portion of the complement by the antigen in a nonspecific manner. Similar results were observed with specimens of sera about three



days old and possessing some anticomplementary activity after heating at 55° C. for fifteen minutes; the results, however, were more irregular than obtained with antigen due to the influence of natural antisheep hemolysin. The result shown in Table I was observed with a hemolysin-free serum.

TABLE I  
THE INFLUENCE OF ANTIGEN AND SERUM UPON DILUTED COMPLEMENT AT ROOM TEMPERATURE (22° C.)

MIXTURES	UNITS OF HEMOLYTIC ACTIVITY OF MIXTURES* AFTER STANDING AT ROOM TEMPERATURE			
	AT ONCE	1/2 HOUR	1 HOUR	2 HOURS
Complement 1:30 + equal part saline	0.2	0.2	0.2	0.3
Complement 1:30 + equal part 1:50 antigen	0.2	0.4	0.4	0.4
Complement 1:30 + equal part 1:10 heated serum	0.2	0.4	0.4	0.4

\*Titrated with an antisheep hemolytic system in a water-bath for one hour.

The experiment shown in Table II was conducted with eighteen syphilitic sera and an antisheep hemolytic system. Each serum was tested in five doses and four sets made up as follows:

- A. Serum first followed immediately by antigen and complement.
- B. Antigen first followed by complement; serum was added one-half hour later.
- C. Serum first followed by complement; antigen was added one-half hour later.
- D. Antigen first followed by serum; complement was added one-half hour later.

The experiment shown in Table III was conducted in a similar manner with an antihuman system.

The primary incubation for both was eighteen hours at 8° C.

The results of these experiments have shown:

1. Stronger complement-fixation reactions frequently result when antigen and complement are mixed and allowed to stand for one-half hour before the addition of serum, than when the three substances are mixed in succession; however the antigen controls sometimes show slight inhibition of hemolysis. These results are ascribed to the greater nonspecific absorption or fixation of complement by antigen under these circumstances than occurs when antigen, complement and serum are mixed in succession.



TABLE III.  
INFLUENCE OF ORDER OF MIXING SERUM, ANTIGEN, AND COMPLEMENT UPON THE RESULTS OF COMPLEMENT-FIXATION REACTIONS  
IN SYPHILIS WITH AN ANTIHUMAN HEMOLYTIC SYSTEM.

A SERUM+ANTIGEN+ COMPLEMENT				B ANTIGEN+COMPLEMENT SERUM 1 HOUR LATER				C SERUM+COMPLEMENT ANTIGEN 1 HOUR LATER				D ANTIGEN+SERUM COMPLEMENT 1 HOUR LATER			
0.1	0.01	0.001	CONTROL	0.1	0.01	0.001	CONTROL	0.1	0.01	0.001	CONTROL	0.1	0.01	0.001	CONTROL
4*	4	—	—	4	4	—	—	4	4	1	±	4	4	1	—
4	2	—	—	4	3	—	—	4	2	—	—	4	3	—	—
4	4	—	—	4	4	—	—	4	4	—	—	4	4	—	—
4	4	—	—	4	4	—	—	4	4	—	—	4	4	—	—
4	1	—	—	4	3	—	—	4	2	—	±	4	2	1	—
4	4	—	—	4	4	—	—	4	4	—	—	4	4	—	—

\* 4 equals + + + +; 3 equals + + +; 2 equals + +; 1 equals +.



TABLE IV.  
THE INFLUENCE UPON COMPLEMENT-FIXATION REACTIONS OF MIXING SERUM AND ANTIGEN FOR VARYING PERIODS OF  
TIME BEFORE THE ADDITION OF COMPLEMENT

SERA	COMPLEMENT ADDED AT ONCE					COMPLEMENT ADDED 5 MINUTES LATER					COMPLEMENT ADDED 15 MINUTES LATER					COMPLEMENT ADDED 60 MINUTES LATER				
	0.1	0.02	0.004	0.00016	CONTROL	0.1	0.02	0.004	0.00016	CONTROL	0.1	0.02	0.004	0.00016	CONTROL	0.1	0.02	0.004	0.00016	CONTROL
	4*	4	2	—	—	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—
Syphilitic.....	1	—	—	—	—	1	1	—	—	—	1	1	—	—	—	1	—	—	—	—
Syphilitic.....	4	4	1	—	—	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—
Syphilitic.....	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
Syphilitic.....	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—
Syphilitic.....	4	4	4	1	—	4	4	4	1	—	4	4	4	1	—	4	4	4	1	—
Syphilitic.....	4	4	1	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
Normal.....	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Normal.....	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

\* 4 equals + + + +; 3 equals + + +; 2 equals + +; 1 equals +.

2. Similar results are sometimes observed when serum and complement are mixed and allowed to stand for at least half an hour before the addition of antigen; the serum controls, however, may show slight inhibition of hemolysis due to the greater nonspecific absorption of complement by serum alone under these circumstances than occurs when the three substances are mixed in succession.

3. When serum and antigen are mixed and allowed to stand for about one-half hour before the addition of complement, the reactions are sometimes (not always) stronger than those in which serum, antigen, and complement are mixed in rapid succession; the antigen and serum controls show complete hemolysis in both sets. The only explanation at hand for this important practical observation, relates to the phenomenon of precipitation which probably occurs when syphilitic serum and lipoidal extracts are brought together under proper conditions.

Additional experiments to determine more accurately the relation of time to this phenomenon have shown that when syphilitic serum and antigen are mixed and allowed to stand at about 22° C. for five to thirty minutes before the addition of complement, stronger reactions are likely to occur than when serum, antigen, and complement are mixed in rapid succession; the results of one experiment are shown in Table IV.

*Accordingly, something is to be gained in the way of increasing the sensitiveness of specific complement-fixation reactions in syphilis by mixing antigen and serum for at least five minutes at ordinary room temperature before completing the test by the addition of complement followed by the primary incubation; stronger reactions may also result by allowing antigen and complement or patient's serum and complement to stand for about half an hour before completing the tests, but these results are due to nonspecific factors which may introduce serious errors in the interpretation of the reactions.*

## Part 2

### THE INFLUENCE OF TOTAL VOLUME

Numerous experiments have shown that the total volume or dilution of complement has an important bearing upon its hemolytic activity. As shown in Table V the unit of a complement diluted 1:30 and titrated with an antishoop system was 0.2 c.c. when saline solution

had been added to give a total volume of 1 to 1.5 c.c., but 0.3 c.c. or more when the total volume was raised to 3 c.c. or higher.

TABLE V

THE INFLUENCE OF TOTAL VOLUME UPON THE TITRATION OF COMPLEMENT 1:30 IN THE PRESENCE OF ANTIGEN\*

UNITS OF COMPLEMENT 1:30 IN TOTAL VOLUMES OF					
1 c.c.	1.5 c.c.	2 c.c.	3 c.c.	4 c.c.	5 c.c.
0.2 c.c.	0.2 c.c.	0.25 c.c.	0.3 c.c.	0.3 c.c.	0.4 c.c.

\*Antisheep hemolytic system.

Likewise in the titration of hemolysin, total volume or dilution may exert an important influence upon hemolytic activity and probably mostly upon complement; this is well shown in the results of an experiment given in Table VI.

TABLE VI

THE INFLUENCE OF TOTAL VOLUME UPON THE TITRATION OF ANTISHEEP HEMOLYSIN

UNITS OF HEMOLYSIN IN TOTAL VOLUMES OF					
1 c.c.	1.5 c.c.	2 c.c.	3 c.c.	4 c.c.	5 c.c.
0.1 of 1:3000	0.1 of 1:2000	0.1 of 1:2000	0.1 of 1:1000	0.1 of 1:1000	0.1 of 1:500

*The point of practical importance is that complement and hemolysin should be titrated in the same total volume as used in the complement-fixation tests; error may result if these are titrated in a given total volume and the units used in main tests with a higher volume.*

TABLE VII

THE INFLUENCE OF TOTAL VOLUME UPON COMPLEMENT-FIXATION REACTIONS IN SYPHILIS

SERA	TOTAL VOLUME 1.5 C.C.						TOTAL VOLUME 4.5 C.C.					
	0.1	0.025	0.006	0.0015	0.0004	CONTROL	0.1	0.025	0.006	0.0015	0.0004	CONTROL
Normal	—	—	—	—	—	—	+	+	+	+	+	—
Normal	—	—	—	—	—	—	+	+	+	+	+	—
Syphilitic	++	+	—	—	—	—	+++	+	+	+	+	—
Syphilitic	+++	—	—	—	—	—	+++	+	+	+	+	—
Syphilitic	++++	++	—	—	—	—	++++	+++	+	+	+	+
Syphilitic	++++	++	—	—	—	—	++++	+++	+	+	+	—
Syphilitic	++	+	—	—	—	—	++++	+++	+	+	+	—
Syphilitic	+++	++	+	—	—	—	++++	+++	++	+	+	—





This fact has been established in numerous experiments, the results of two being given in Tables VII and VIII as examples. In both experiments the complement (diluted 1:30) and hemolysin were titrated in a total volume of 2 c.c. and used in two units for comparative complement-fixation tests in which the total volumes varied from 1.5 c.c. to 5 c.c.

As shown in these tables, complement-fixation tests conducted with total volumes double or more than used in the titration of complement, showed incomplete hemolysis and proved unsatisfactory; the higher dilutions showed most interference with hemolysis.

In building up the technic of a complement-fixation test it is necessary to decide upon the total volume of fluid according to the depth of color desired, convenience and such factors, but it *should be a principle of technic that the complement is titrated in the same total volume (same final dilution) as used in the main complement-fixation tests*; slight differences in dilutions make no difference in the results but great differences interfere with hemolysis and particularly if the complement is highly diluted (1:30), as used in these experiments.

#### CONCLUSIONS

1. In setting up complement-fixation tests for syphilis, serum and antigen should first be placed in test tubes followed after an interval of five to thirty minutes by complement, saline solution and the primary incubation; this technic occasionally results in somewhat more sensitive specific reactions than observed when serum, antigen, and complement are mixed in rapid succession.

2. Antigen and complement should not be mixed and allowed to stand before the addition of patient's serum, because of the increased nonspecific fixation of complement by antigen alone under these circumstances.

3. Patient's serum and complement should not be mixed and allowed to stand before the addition of antigen, because of the increased nonspecific fixation of complement by serum alone under these conditions.

4. Total volume or dilution has an important bearing upon the hemolytic activity of complement; for this reason the complement and hemolysin should be titrated in the same dilution (total volume) as used in the conduct of complement-fixation tests.

## THE VALUE OF ICE BOX INCUBATION AND CHOLESTERIN ANTIGEN AS SHOWN BY 1600 COMPARATIVE TESTS\*

By B. W. RHAMY, M.D., FORT WAYNE, INDIANA

(Received for publication, November 30, 1920.)

THE purpose of this paper is to set forth my personal experience with the newer Wassermann procedures; namely, ice box incubation coupled with cholesterolin antigen, in a series of 1600 comparative tests. In this series, comparisons were made by making two complete tests on each serum, one by the regular heat incubation method, and one by ice box incubation, and using two antigens in both. Before proceeding with a discussion of this data, it seems proper to outline the Wassermann technic followed. The antihuman system was used throughout, as in my opinion, the fluctuating amount of natural antishoop amboceptor to be found in human blood, is a factor which may influence the test decidedly. Guinea pig complement was prepared thus: A pool was made from all the blood of four or five guinea pigs, the serum separated immediately after clotting and preserved in the form of a 40 per cent dilution using as a diluent and preservative 10 per cent sodium acetate in distilled water. This preservative was reported by me in *Jour. Am. Med. Assn.*, Sept, 22, 1917, and again June 29, 1918. I now add to it 2 drops of Toluol to each 5 c.c. of fluid. Complement thus preserved works well, giving good fixation for from two to three weeks. For use this 40 per cent dilution was further diluted with sterile normal salt solution to 5 per cent (1-20) or to 10 per cent (1-10), depending on its strength. The unit was determined each day before use in this manner: To each of a series of tubes was added two drops (.1 c.c.) of inactivated normal serum and two units of glycerinated antihuman amboceptor, .1 c.c. of 5 per cent cell emulsion and graduated amounts of 1-20 or 1-10 complement dilution beginning with .05 c.c. and stepping up .05 or .1 per tube depending on the activity of the complement, as previously tested. Then enough normal salt solution to total 1 c.c. in each tube. These

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\*Read before the Twelfth District Medical Society, Fort Wayne, Indiana, Nov. 9, 1920.



racks were incubated two hours at 37° C. and if necessary, centrifuged to locate the exact point to complete hemolysis. This represented one unit, two such units being used for each tube in the Wassermann racks.

Five per cent emulsions of human blood cells were prepared from a pool of four or five samples of blood for the reason that, as I pointed out in the Jour. Am. Med. Assn., Nov. 17, 1917, individual specimens of blood vary in hemolytic resistance just as guinea pig complement varies in strength. The pool of cells I find prevents this fluctuation, thereby keeping the unit of preserved complement more constant. The cell emulsions were preserved in .125 per cent formalin in normal salt solution and were used until they began to hemolyze, usually four or five days. One tenth c.c. of this 5 per cent emulsion was the dose for each tube, one front tube containing either acetone-insoluble antigen or alcoholic extract of luetic liver (in this paper I shall refer to either of these as alcoholic extract antigen), the other cholesterinized alcoholic extract of syphilitic liver antigen and one back tube without antigen for the hemolytic control. Four drops (.2 c.c.) of inactivated serum was the standard dose of serum. As controls, tubes were set in the same way from known inactivated normal and luetic serums which I had conveniently preserved by adding two drops of Toluol per 5 c.c. of serum. Toluol is, in my opinion, the best preservative for serum. Although the serum may become somewhat emulsified after its addition, this does not interfere with the test and the serum remains sweet and clean. After a while, if kept long enough, it may become milky white and then it should be discarded for it will be hemolytic. I have tried preserving serums with glycerol as recommended by Ruediger, but abandoned it on account of its tricky quality of suddenly becoming anticomplementary and this I found might happen either at an early or late date. Two sets of racks were used duplicating each test and incubated as follows: One rack was incubated at 37° C. for one hour; cells and amboceptor were then added and then incubated for two hours. The other rack was placed in the ice box at 8° C. for eighteen hours, or overnight; cells and amboceptor added and then incubated at 37° for two hours. In reading results the plus signs are used, each plus mark representing approximately 25 per cent inhibition, four plus meaning complete inhibition, or 100 per cent. A doubtful or plus minus ( $\pm$ ) is understood to mean less than 15 per cent inhibition or 85 per cent hemolysis.

I might also add that I have always considered my (++) two plus reaction by heat with alcoholic or acetone-insoluble antigen as diagnostic of syphilis and (+) one plus by these antigens or (++) two plus or less by cholesterin antigens as being doubtful. In the consideration of this data, I start on these premises, that, as reported by other writers cholesterinized antigen gives about 10 per cent more positives than does alcoholic extract or acetone-insoluble antigen and, that, ice box incubation also gives about 10 per cent more positives with alcoholic extract antigen than does the heat method. With this assumption in mind, I report that in a series of 1600 tests there were 11 atypical or paradoxical reactions, i. e., 11 sera that either gave a positive or doubtful reaction by heat and showed a weaker reaction in the ice box; or were positive by alcoholic or acetone-insoluble antigens and negative by cholesterinized antigen. These were either so-called paradoxical reactions or were errors in the technic. If we assume the latter then this would amount to a little less than .68 of 1 per cent error, as against the above assumption. It has been said too, that cholesterin antigen was too sensitive, giving some reactions in nonsyphilitics.

Particular interest then lies in what the ice box does with the sera which reacted negatively to simple antigen and doubtful or positive to cholesterinized antigen by the heat method. Of the 1600 tests 858 or 57.7 per cent were negative by both methods; 675, or 42.3 per cent, were, then, either doubtful or positive; 244, or 15.3 per cent, of these reacting sera showed the same positive reaction by both methods, i. e., when heat showed (++++) the ice box of course could but record the same; 318, or 20 per cent, showed stronger reactions in the ice box; 350 or 21.8 per cent were definitely positive by the heat method while 552, or 34.5 per cent, were definitely positive by the ice box method, giving 202, or 12.6 per cent, more positives by the ice box. Of these 42, or 2.6 per cent, were negative by heat and definitely positive by the ice box and the remaining 144 were doubtful by heat and definitely positive by the ice box = 9 per cent.

You will note that 57 per cent were negative by both methods and 15.3 per cent showed (++++) or complete reaction by both methods, making 73 per cent of all tests having the same reactions which on account of their nature could not be stronger in the ice box. There remains 27 per cent which having weak reactions by heat should, if

they are luetic, and if the theory of mass action be true, show stronger reactions by ice box. Looking on Chart 2 we find that 20 per cent of all tests were stronger in the ice box, i. e., practically all of the 27 per cent; the difference being doubtful reactions of the ice box (0 0).

(0 ++)

Coming now to the antigens (see Chart 3) I find that 282, or 17.6 per cent, gave stronger reactions in the ice box to alcoholic antigen and that 306, or 20.2 per cent, gave a stronger reaction by cholesterolin antigen in the ice box, showing practically the same increase for both alcoholic and cholesterolin antigen. Ninety-four, or 5.8 per cent, were negative to alcoholic antigen by heat and positive to cholesterolin antigen by heat. Thirty-two, or 2 per cent, were negative to alcoholic antigen by both methods and positive to cholesterolin by both methods. Forty-two, or 2.6 per cent, were negative by heat to both antigens and positive by both in the ice box. Sixty-one, or 3.8 per cent, were negative to alcoholic antigen and positive to cholesterolin by heat and positive to both antigens by ice box. Fifty-one, or 3.1 per cent, were doubtful by alcoholic antigen and positive by cholesterolin antigen by heat and were positive to both in the ice box.

It is obviously impossible in a public laboratory to associate figures with complete clinical data. However, I am able to present 641 cases for comparison with clinical data. Among these were 62 cases diagnosed clinically as syphilis. Of course, these could not all be called "known syphilis," as there must naturally be a certain percentage of error in such diagnosis.

Seven of these were negative by both methods = 11.4 per cent; 55 of these were doubtful or positive by the ice box = 88.7 per cent; 46 of these were definitely positive by heat = 72.8 per cent; 51 of these were definitely positive by ice box = 82.6 per cent, netting 10 per cent more positives by the ice box. Of this 10 per cent, or 6 cases, one was negative and 5 were doubtful by heat. One case, or 1.6 per cent, showed a paradoxical reaction; 19 tests, or 26.4 per cent, showed a stronger reaction by ice box. Six cases, or 10 per cent, were negative or doubtful by heat to alcoholic antigen and positive by heat to cholesterolin antigen and positive by both in the ice box.

In 185 cases of known syphilis under treatment, 82, or 44.3 per cent, had been rendered negative, the average length of treatment being 2 years. Forty, or 21.6 per cent, were positive by heat, while



77, or 41.6 per cent, were positive in the ice box, making 37 or 20 per cent which would have been considered negative or doubtful by the heat method, but showed positive by the ice box. Of these, 11 cases or 5.94 per cent were negative and 25 cases, or 13.3 per cent, were doubtful by heat. In these cases the average length of treatment was 1 year, and the average number of salvarsan injections 7. Forty-eight tests, or 26.6 per cent, showed stronger by both alcoholic and cholesterin antigen in the ice box. Thirteen cases, or 7 per cent, were negative by heat to alcoholic antigen, but positive to cholesterin antigen and positive by both antigens in the ice box. Eight cases, or 4.3 per cent, were negative to alcoholic antigen by both heat and ice box methods and positive to cholesterin antigen by both methods.

In all, 90 cases, or 48.7 per cent, after an average of 1 year's treatment and 7 doses of salvarsan were either doubtful or positive by ice box, indicating further treatment, while by the heat method 11 of these might have been considered cured.

In 125 cases showing suspicious symptoms, 51, or 40.8 per cent, were negative by both methods. Forty-six cases, or 36.8 per cent, were positive by heat, while 61 cases, or 48.8 per cent, were positive by ice box, making 12 per cent more positives by ice box. Of these, 4, or 3.2 per cent, were negative and 11, or 9 per cent, were doubtful by heat. Twenty-nine cases, or 23.5 per cent, showed stronger reactions by the ice box.

In 149 cases showing vague lesions and with nothing to indicate syphilis but undergoing routine Wassermanns, 105, or 70.4 per cent, were negative by both methods and 44, or 29.6 per cent, were either doubtful or positive by the ice box. Of these 20, or 13.4 per cent, were positive by heat while 29 cases, or 19.4 per cent, were positive by ice box, making 6 per cent more positives by the ice box. Of these, 2 cases, or 1.4 per cent, were negative and 9 cases, or 6 per cent, were doubtful by heat. Seventeen cases, or 11.6 per cent, showed stronger reactions by ice box.

In 44 cases with suspicious history, such as possible heredity, marriage to a luetic, etc., but with no symptoms, there were 22, or 50 per cent, negative by both methods and 22, or 50 per cent, doubtful or positive by ice box. Eleven cases, or 25 per cent, were positive by heat while 17 cases, or 38.6 per cent, were positive by ice box, making 6, or 13.1 per cent, more positives by ice box. These 6 were all

doubtful by heat. Eleven cases, or 24.6 per cent, showed stronger reactions by ice box.

In 76 cases with no symptoms or history (eugenic test) there were 65, or 85.5 per cent, negatives; 11 cases, or 15 per cent, were doubtful or positive by ice box; 4, or 5.2 per cent, were positive by heat while 7, or 9.2 per cent, were positive by ice box, making 4 per cent more positives by ice box.

#### SUMMARY

It is quite apparent from the survey of these charts that ice box incubation is uniformly more sensitive, the average in this series being 12.6 per cent more positive reactions, while in general 20 per cent, or 1/5 of all reactions were stronger in the ice box. The highest degree of sensibility, 20 per cent, is obtained in known cases of syphilis under treatment, and next with 13.1 per cent are those giving a history of possible heredity, luetic marriage, etc. The lowest figure, 2 per cent, obtained in cases where there is no history or symptoms to give rise to a suspicion of the presence of syphilitic antibodies. Now the theory of ice box incubation is based on the idea that where there is only a trace of syphilitic antibodies, a short incubation period may not produce appreciable fixation of complement, whereas, a longer period of incubation will allow fixation, the reaction evidently following the law of mass action, the antibody, as pointed out by Simon, *Jour. Am. Med. Assn.*, May 24, 1919, apparently entering into combination with complement and antigen but being released immediately to bind other units of complement. If this be true, then it would be in just such cases, that is, in those having had treatment or in those wherein the organism had lost virulence, by hereditary transmission through generations, etc., where the greatest value would obtain and vice versa, where there is no evidence of syphilis and therefore less possibility of the presence of antibodies in any dilution the percentage would be less, which again corresponds to the above figures. This 20 per cent, then, of the cases under treatment would have been pronounced negative with the heat method, whereas they really needed further treatment.

In the cases diagnosed clinically as syphilis, the ice box showed a general average of 82.6 per cent positives, an increase of 9.8 per cent over the heat incubation. A careful scrutiny of these cases with

CHART 1

HEAT AND ICE BOX INCUBATION SUMMARY OF PERCENTAGES	NUMBER OF TESTS	PARADOXICAL REACTIONS		NEGATIVE BY BOTH METHODS		TOTAL POSITIVE BY HEAT		TOTAL POSITIVE BY ICE BOX		Increased Sensibility by Ice Box
		HEAT	ICE	HEAT	ICE	HEAT	ICE	HEAT	ICE	
Symbols	Ale. Antigen	++	+++	0	0	++			++	
		0	0							
	Choles. "	++	0	0	0	+++			+++	
		+++	0							
Whole Series	1600	.68%		57.7%		21.8%		34.5%		12.6%
Clinically Syphilis	62	1.6%		11.4%		72.8%		82.6%		9.8%
Cases with Suspicious Symptoms	124	0		40.8%		36.8%		48.8%		12. %
Treated cases average of 1½ yrs.	185	0		45.3%		21.6%		41.6%		20. %
Suspicious history but no symptoms. Heredity	44	4.3%		40. %		25. %		38.6%		13.1%
—marriage—etc.	149	0		70.4%		13.4%		19.4%		6. %
Cases with Vague lesions										
No symptoms										
No history (eugenic test)	76	0		85.5%		5.2%		9.2%		4. %
Average percentage of clinical cases	Total clinical cases 641	.98%		50.5%		29.1%		40. %		10.8%



CHART 2

SHOWING GENERAL RESULTS	NUMBER OF TESTS	SAME REACTIONS BY BOTH METHODS		REACTIONS STRONGER BY ICE BOX IN		ALCOHOLIC ANTIGEN STRONGER BY ICE BOX IN		CHOLESTERIN ANTIGEN STRONGER BY ICE BOX IN	
		HEAT	ICE	HEAT	ICE	HEAT	ICE	HEAT	ICE
Symbols	Alc. Antigen	+++	+++	++	+++	++	+++	++	+++
	Choles.	+++	+++	+++	+++	++	+++	++	+++
<b>Whole Series</b>	<b>1600</b>	<b>15.3%</b>		<b>20. %</b>		<b>17.6%</b>		<b>20.2%</b>	
Clinically syphilis	62	<b>54.8%</b>		<b>26.4%</b>		<b>27.4%</b>		<b>24.2%</b>	
Cases with suspicious symptoms	125	26. %		23.5%		22.5%		21.8%	
Treated cases average of 1½ yrs.	185	14.6%		<b>26.6%</b>		<b>30.2%</b>		<b>33. %</b>	
No symptoms, suspicious history, heredity—etc.	44	20.4%		24.9%		31.8%		29.3%	
Cases with vague lesions	149	10. %		11.6%		13.4%		14.7%	
No History									
No Symptoms (eugenic tests)	76	4. %		6.6%		2.6%		7.7%	
<b>Averages of clinical cases</b>	<b>Total clinical cases 641</b>	<b>21.6%</b>		<b>20. %</b>		<b>21.3%</b>		<b>21.8%</b>	



a view of refining the diagnosis, and the exclusion thereby of one case of paresis in which the spinal fluid was positive, (in which cases we often expect a negative blood) and of two cases of chancre under ten days old, the percentage of ice box positives in known syphilis runs up to 86.4 per cent. Heretofore ice box figures reported applied principally to alcoholic antigen. In this series cholesterin antigen showed about the same increase in sensibility in the ice box.

This, by the way, should obtain, for there is no reason why the mass action principle should work on alcoholic extract antigen and not on any other antigen. Viewing now the action of cholesterin antigen, we find in Chart 3 that of those tests where cholesterin antigen alone was positive by both methods, the highest percentage, 4.3 per cent, was in treated cases. In those tests where by heat, alcoholic antigen was negative and cholesterin positive, while both were positive in the ice box, the highest percentage includes treated cases (8 per cent) and those with suspicious history (9 per cent), those having suspicious symptoms next with 5.7 per cent, and those clinically syphilis next with 3 per cent. In the tests wherein alcoholic antigen showed strongest by ice box, we again find the highest percentage 30.2 per cent in cases under treatment, and in those with suspicious history with 31.8 per cent and those clinically syphilis next with 27.4 per cent. Cholesterin antigen gave stronger reactions by ice box in the same sort of cases and in about the same percentage as did alcoholic antigen, i. e., treated cases 33 per cent; cases with suspicious history 29.3 per cent, and cases clinically syphilis 24.2 per cent.

One striking feature of these charts is that the series of cases having no symptoms or suspicious history without exception give either straight positives or negatives, i. e., none of the odd or atypical reactions and especially with cholesterin antigen as shown in Chart 3. It will be noted, therefore, that the atypical reactions in general, i.e.,

such as  $\begin{pmatrix} 0 & 0 \\ ++ & ++ \end{pmatrix} - \begin{pmatrix} 0 & ++ \\ 0 & +++ \end{pmatrix} - \begin{pmatrix} 0 & ++ \\ + & +++ \end{pmatrix}$  are to be found in the

cases where syphilitic antibodies are likely to be found in small amounts, and especially in cases under treatment. It is my idea that the treatment in some manner disintegrates or changes the antibodies in some way so that they may be either loosely bound, or not at all, in a sort of haphazard way.

Now taking these cases as a whole, i.e., the last three columns of



Chart 3 giving negative or doubtful reactions to alcoholic antigen by heat, doubtful or positive reactions to cholesterin antigen by heat of which there are 8.9 per cent of the whole series, it will be noted that the greatest number occur in cases under treatment, 17.5 per cent of which gave these reactions. Thirteen per cent of these cases with no symptoms but suspicious history and 11.3 per cent of those having suspicious symptoms also gave such reactions. Of the total number of reactions of this kind 78.6 per cent of *them* were definitely positive in the ice box to both antigens and as noted were mostly treated cases, those with suspicious histories and those with suspicious symptoms. The remainder, 21.4 per cent, which gave the same reaction by the ice box as by heat  $\begin{pmatrix} 0 & 0 \\ ++ & +++ \end{pmatrix}$  were also, mostly in these kind of cases.

To sum up, the charts show that the more likelihood of syphilis and the more abundant the antibodies, the more frequent and more typical the reactions, and vice versa; i.e., that the atypical and cholesterin reactions (shown in Chart 3) occur mostly in those cases where only a trace of antibodies might be expected. That the series of eugenic tests in which syphilis is not to be expected is so free from atypical reactions, adds proof to this argument. Another point of interest is that the average percentage in the clinical cases shown at the bottom of the charts closely imitate those of the whole series, so much so that I feel warranted in assuming that if I had the clinical findings for the whole series, the figures would average about the same. Incidentally the chart shows paradoxical reactions only in cases diagnosed clinically as syphilis and in cases under treatment, the percentage in the latter being quite large (4.3 per cent).

#### CONCLUSION

The Wassermann test, if done in the ice box, is in general about 12.6 per cent more sensitive than the heat method, and, therefore, just that many per cent more accurate. The ice box also shows that most of the doubtful reactions by heat, and especially where the cholesterin antigen is positive by heat, indicate traces of syphilis. And finally, one lesson to be learned from a survey of these charts, is that a better judgment can be formed of the meaning of the result where both heat and ice box figures are given than where only either one or the other is reported.

The last two clinical classifications on the chart (vague lesions and eugenic tests) including as they do, cases having no history or suspicious symptoms giving rise to a suspicion of syphilis show in the ice box 28.6 per cent as definitely positive, which means that 28.6 per cent of them had syphilis and did not know how they got it.

The use of sodium acetate as a complement preservative allows longer periods of primary incubation as its stabilizing qualities prevent rapid deterioration of complement when subjected to heat.

## ICE WATER-BATH IN COMPLEMENT FIXATION FOR THE WASSERMANN REACTION—A SHORTENED TECHNIC

BY W. W. DUKE, M.D., KANSAS CITY, MO.

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THE refrigeration or ice box method of complement fixation for the Wassermann reaction introduced by Jacobstahl<sup>1</sup> (1910) and Guggenheimer<sup>2</sup> (1911) and popularized by McNeil,<sup>3</sup> Altman,<sup>4</sup> Walker and Swift, Smith and MacNeal,<sup>5</sup> Ruediger<sup>6</sup> and others marks the chief advance in Wassermann technic since the introduction of cholesterinized antigen. The refrigeration method has been used in this laboratory almost exclusively during the past three and one-half years. During this period over fifty thousand tests have been carried out on more than ten thousand different specimens of blood. The ice box method has been run in parallel with the 37.5° C. incubator method from time to time. Our results harmonize with those reported in the literature showing that the refrigeration method is much more delicate than the warm water incubation method and we believe it will be adopted generally in the course of time.

A serious objection to the refrigeration method has been the time required (4 hours) for incubation. This makes the ice box Wassermann technic require in all about seven hours time. By using an ice water-bath instead of an ice box, we have been able to shorten the time for incubation to one hour without materially altering its result. We wish, therefore, to report briefly this modification of the method with a few typical examples of reactions which were carried out simultaneously by the warm water-bath, ice box and ice water-bath technic.

### METHOD

According to the original refrigeration technic, the tubes are set up with antigen, complement and blood to be tested and placed in the ice box at approximately 9° C. for four hours' incubation, after which time the sensitized cells are added and the tubes incubated at 37.5° C. in a water-bath for one hour when the readings are made. By the modified technic to be described, the tubes are set up according to



a method to be described subsequently and are placed in a rectangular galvanized iron pan with stopcock for drainage. Ice water is poured into the pan until it reaches a level higher than that of the fluid in the tubes. The temperature of this water is kept at 8° C. for fifteen minutes by the addition of small pieces of ice. (The temperature of a tube placed in the ice water-bath is reduced to 9° C. in five minutes or less.) After the expiration of fifteen minutes, the ice is removed with the result that the temperature of the ice water-bath rises approximately one degree each half hour. At the end of the hour, the ice water is drawn off by opening the stopcock and the pan is refilled with water at 40° C. The tubes are allowed to remain in this for a period of five to ten minutes in order to remove the chill from the tubes before they are placed in the 37.5° C. water-bath. The sensitized cells are then added and the tubes are placed in the 37.5° C. water-bath for one hour at which time the readings are made. The above details are important. If the tubes are not warmed before they are placed in the warm water-bath, the warm water-bath is cooled down with the result that the complement acts too slowly and may make the control tubes simulate the reaction of an anticomplementary serum.

For the past year a five tube test has been used in this laboratory which is set up as follows:

All tubes contain amboceptor (antisheep) two units, patient's blood serum 1/20 c.c., sheep cells 0.2 c.c., of a 5 per cent suspension, antigen 1/5 the anticomplementary amount or less, salt solution to a total volume of 1.25 c.c.

Tube 1	contains,	antigen	cholesterinized	.4%,	complement	1 unit.
Tube 2	"	,	"	.2%	"	1 "
Tube 3	"	,	"	.2%	"	2 "
Tube 4	"	,	Acetone insoluble		"	2 "
Tube 5	"	,	Alcohol extract		"	2 "

The advantages of this set up are as follows: Tube 1 is so sensitive that it comes out positive in the overwhelming majority of specific cases whether active or latent. This tube, therefore, is useful in excluding syphilis in the general diagnosis of a medical case. We find very few cases of syphilis which can be diagnosed clinically or by spinal puncture which do not give a positive reaction in Tube 1. This tube gives a considerable number of false positives, in fact, it

gives a 4+ reaction in 33 per cent of the medical cases examined as a routine in this clinic without regard to complaint. (Bloods sent in for Wassermann reactions because of suspected syphilis are excluded from these statistics.) As previously mentioned, this tube is used for the purpose of excluding syphilis in the routine diagnosis of a medical case, not in its diagnosis. Tube 2 is also very sensitive although less so than Tube 1. In fact, it is only about one-fifth as sensitive as Tube 1. However, Tube 2 also gives a number of false positives and gives a 4+ reaction in 22 per cent of general medical cases. This test is also used in excluding syphilis, not in its diagnosis. Tube 3, which contains two units of complement, is less sensitive than Tube 1 or 2. It gives fewer false positives. Blood which gives a  $\pm$  reaction in Tube 3 gives a 4+ reaction in Tubes 1 and 2. A 4+ reaction in this tube is not often found in anything other than specific cases. Tubes 1, 2 and 3 come out 4+ in 19 per cent of general medical cases, Tubes 4 and 5, in which two units of complement are used and the antigen is noncholesterinized, are still less sensitive than Tubes 1, 2 and 3. We have no record of these two tubes giving false positives. They come out 4+ in 13 per cent of general medical cases.

It is interesting to compare the reactions of doubtful and weak positive bloods carried out by the three technics, that is, the warm water-bath, the ice box, and the ice water-bath. We have run a great number of parallel tests in this way in the laboratory and find that the ice water-bath and ice box give almost identical results and give invariably a much more complete fixation than the warm water-bath. They are each approximately five times as sensitive as the warm water-bath method. Several typical examples are given in the accompanying tables.

TABLE I  
A DOUBTFUL REACTION (TREATED CASE)

TUBE NUMBER	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1	-	4+	4+
2	-	4+	4+
3	-	-	-
4	-	-	-
5	-	-	-

TABLE II  
A WEAK POSITIVE REACTION (TREATED CASE)

TUBE NUMBER	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1	4+	4+	4+
2	4+	4+	4+
3	-	4+	4+
4	-	2+	2+
5	-	1+	2+

TABLE III  
POSITIVE BLOOD (TREATED CASE)

TUBE NUMBER	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1	4+	4+	4+
2	4+	4+	4+
3	4+	4+	4+
4	-	4+	4+
5	-	4+	4+

It is interesting to point out in the above tables that the blood used in Table I gave a completely negative test by the warm water-bath technic and gave 4+ reactions with cholesterinized antigen and one unit of complement by both refrigeration methods. The blood used in Table II was too weakly positive to inhibit two units of complement by the warm water-bath and gave negative tests in Tubes 3, 4 and 5. It gave 4+ reactions in Tube 3 by the refrigeration methods and a 1+ and 2+ with noncholesterinized antigens. The blood used in Table III was too weakly positive to show any inhibition with noncholesterinized antigens (Tubes 4 and 5) when incubated at 37.5° C. but gave a 4+ reaction in these tubes by the refrigeration methods. The above tests are typical examples of reactions given by doubtful or weakly positive bloods.

A clearer conception of the delicacy of the tests can be gained by an examination of Tables IV, V, VI and VII in which several strong positive bloods are titrated and tested by the three methods. In these titrations, cholesterinized antigen, .2 per cent was used, 2 units of complement in Tables IV and V and 1 unit of complement in Tables VI and VII.

It can be seen in Tables IV to VII that the refrigeration methods (Ice box four hours and ice water-bath one hour) give almost iden-



TABLE IV  
TITRATION OF RELATIVELY STRONG POSITIVE SERUM (2 UNITS COMPLEMENT)

SERUM	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1/30 c.c.	4+	4+	4+
1/60 c.c.	4+	4+	4+
1/100 c.c.	4+	4+	4+
1/200 c.c.	1+	4+	4+
1/500 c.c.	-	4+	4+
1/1000 c.c.	-	4+	3+
1/2000 c.c.	-	-	-

TABLE V  
TITRATION OF STRONG POSITIVE SERUM (2 UNITS COMPLEMENT)

SERUM	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1/30 c.c.	4+	4+	4+
1/60 c.c.	4+	4+	4+
1/100 c.c.	4+	4+	4+
1/200 c.c.	4+	4+	4+
1/500 c.c.	1+	4+	4+
1/1000 c.c.	-	4+	4+
1/2000 c.c.	-	3+	3+
1/3000 c.c.	-	1+	1+
1/5000 c.c.	-	-	-

TABLE VI  
TITRATION OF WEAK POSITIVE SERUM (1 UNIT COMPLEMENT)

SERUM	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1/30 c.c.	4+	4+	4+
1/60 c.c.	4+	4+	4+
1/100 c.c.	4+	4+	4+
1/250 c.c.	1+	4+	4+
1/500 c.c.	-	4+	4+
1/1000 c.c.	-	1+	1+
1/2000 c.c.	-	-	-

TABLE VII  
TITRATION OF STRONG POSITIVE SERUM (1 UNIT COMPLEMENT)

SERUM	WARM WATER-BATH 1/2 HOUR	ICE BOX 4 HOURS	ICE WATER-BATH 1 HOUR
1/30 c.c.	4+	4+	4+
1/60 c.c.	4+	4+	4+
1/100 c.c.	4+	4+	4+
1/250 c.c.	4+	4+	4+
1/500 c.c.	4+	4+	4+
1/1000 c.c.	1+	4+	4+
1/2000 c.c.	-	4+	4+
1/4000 c.c.	-	-	2+
1/5000 c.c.	-	-	1+
1/8000 c.c.	-	-	-

tical results and that both are five times or more as delicate as the warm water-bath method. These are typical examples and represent average results obtained in many comparative titrations. It seems unnecessary to report more examples.

The question which finally arises concerns whether or not one hour's incubation in the ice water-bath gives a finished reaction; in other words, whether or not incubation for a longer period of time or by a different method would give a more complete fixation. To discover if this might be the case, a number of comparative titrations were made in which different methods of incubation were used. It was found that none give a more complete fixation than that obtained by one hour's ice water-bath incubation.

For example, in several series of titrations, the tests were incubated one hour, two hours, four hours and overnight in the ice water-bath. The results obtained were almost identical.

One of this set is reported in Table VIII. It can be seen that with both the noncholesterinized and cholesterinized antigen, the reaction obtained is about the same whether the tests were incubated one, two or four hours respectively. This result was somewhat different from that obtained by incubating bloods for varying periods of time in the warm water-bath. Blood incubated for one-half hour in the warm water-bath does not give as strong a reaction as when incubated for a period of one, two or four hours. In fact, four hours' incubation in the warm water-bath gives a reaction which is definitely stronger than that obtained by one-half hour's incubation. We believe therefore that one-half or one hour's incubation in a warm water-bath is inadequate.

We also made comparative titrations, incubating first in the ice water-bath for one hour and following this incubating in the warm water-bath for one hour; also by incubating one hour in the ice water-bath and then allowing the temperature of the water-bath to rise gradually during a period of nine hours to room temperature and finally incubating one additional hour in the warm water-bath. The results obtained by these methods were little or no more complete or positive than that obtained by one hour's incubation in the ice water-bath. We believe, therefore, that the fixation obtained by one hour's ice water-bath incubation is complete and adequate and is as good as that which can be obtained by any method with which we are acquainted at the present time.

TABLE VIII

Titration of a positive serum comparing the incubation in an ice water-bath for one, two and four hours. In all tubes two units of complement were used. In series A, cholesterinized antigen was used and in series B noncholesterinized antigen was used.

INCUBATION Series Antigen SERUM	ONE HOUR		TWO HOURS		FOUR HOURS	
	A .2% Chol.	B Nonchol.	A .2% Chol.	B Nonchol.	A .2% Chol.	B Nonchol.
1/30 c.c.	4+	4+	4+	4+	4+	4+
1/60 c.c.	4+	4+	4+	4+	4+	4+
1/100 c.c.	4+	4+	4+	4+	4+	4+
1/130 c.c.	4+	3+	4+	3+	4+	3+
1/160 c.c.	4+	-	4+	-	4+	-
1/200 c.c.	4+	-	4+	-	4+	-
1/260 c.c.	4+	-	3+	-	3+	-
1/340 c.c.	2+	-	2+	-	1+	-
1/500 c.c.	-	-	-	-	-	-
1/750 c.c.	-	-	-	-	-	-

TABLE IX

Titration of the same blood used in Table VIII comparing incubation in the warm water-bath at 37.5° C. for one-half hour, one hour, two and four hours with the same antigen and complement as used in Table VIII.

INCUBATION Series Antigen SERUM	ONE-HALF HOUR		ONE HOUR		TWO HOURS		FOUR HOURS	
	A .2% Chol.	B Non-chol.	A .2% Chol.	B Non-chol.	A .2% Chol.	B Non-chol.	A .2% Chol.	B Non-chol.
1/30 c.c.	4+	4+	4+	4+	4+	4+	4+	4+
1/60 c.c.	4+	4+	4+	4+	4+	4+	4+	4+
1/100 c.c.	4+	3+	4+	4+	4+	4+	4+	4+
1/130 c.c.	4+	2+	4+	1+	4+	3+	4+	3+
1/160 c.c.	2+	-	3+	-	4+	1+	4+	-
1/200 c.c.	1+	-	2+	-	3+	-	4+	-
1/260 c.c.	-	-	1+	-	3+	-	3+	-
1/340 c.c.	-	-	-	-	2+	-	2+	-
1/500 c.c.	-	-	-	-	-	-	-	-
1/750 c.c.	-	-	-	-	-	-	-	-

## CONCLUSIONS

1. The use of an *ice water-bath* for *one hour* for complement fixation for the Wassermann test gives as complete a degree of complement fixation as incubation in the *ice box* for *four hours*. The use of an *ice water-bath*, therefore, shortens the refrigeration technic three hours without altering its accuracy. For this reason its use is recommended.



2. I acknowledge with pleasure the expert assistance in this work of Miss Elizabeth Leas, technical laboratory assistant.

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THE WASSERMANN REACTION: REASONS FOR DISCREP-  
ANCIES IN ESTIMATION OF CLINICAL VALUE:  
NECESSITY FOR UNIFORMITY AND STANDARDI-  
ZATION: SUGGESTIONS: REPORT OF A  
SERIES AND INTERPRETATION\*

BY HENRY M. RAY, M.D., PITTSBURGH, PA.

*Pathologist, South Side Hospital*

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IN the April 17, 1920, number of the *Journal of the American Medical Association*, an editorial entitled "Accuracy of the Wassermann Test" reviews the conclusions of Dr. Hubert Turnbull of the Pathologic Institute of the London Hospital and Dr. Douglas Symmers of Bellevue Hospital, New York, each of whom presented a series of serological data in conjunction with definite postmortem findings. One is immediately struck by the diversity of opinion regarding the accuracy and clinical value of the Wassermann test and the editor very justly concludes with the paragraph, "Here, then, is a wide divergence of opinion, based in each instance, on an apparently accurate scientific investigation. The subject obviously is susceptible to further study."

In this connection, it is worthy of note that in the last three years, a number of articles have appeared reporting inconsistencies between the results of different laboratories on the Wassermann reactions of identical specimens of blood. Such reports, together with the diverse conclusions regarding the value of the reaction, must eventually result in diminishing our confidence in the Wassermann reaction, an outcome which is already beginning to manifest itself among clinicians. As early as 1915, Dr. Emerson then deputy commissioner of the New York City Health Department, principally for the reason of the medicolegal importance of the Wassermann test in its effect on the examination of food handlers, summoned a committee to consider

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the entire question of the reliability of the Wassermann reaction and to attempt to standardize the technic. This committee composed of serologists from the larger New York institutions, obtained some interesting results, but unfortunately the work was not completed. The greatest difficulty encountered was that hardly any two of the twelve men on the committee could precisely agree in the technic for any single step in the reaction, in spite of the fact, that each individually, felt that he was performing the reaction according to classic and well-recognized principles. In spite of this, however, it must be mentioned that the committee was practically unanimous in the belief, that with very few exceptions which in our climate are easily excluded, the Wassermann is reliable and diagnostic of syphilis; that most of the contradictory reports received from different laboratories were cases of syphilis having weak reactions which were detectable only by certain delicacies in technic and that with proper precautions, false positive reactions are avoidable.

Although it is not practical for the clinician to acquaint himself with the finer details of the reaction, there are certain things which he must know, in order to be in a position to properly interpret the results in the laboratory, more particularly in that very important and not infrequent type of case where the reaction is doubtful or where the results with the various antigens are not in accord. It is the object of this paper to emphasize those essential points in the final interpretation from the standpoint of the clinician.

One has but to note the multitude of modifications of the Wassermann reaction to be impressed with the fact, that we have not as yet reached a most perfected laboratory method for the diagnosis of syphilis. There are the modifications of Noguchi, Craig, Bauer, Hecht-Weinberg-Gradwohl, Stern, Tchernogubon, Detre-Brezovsky, Browning-Mackenzi and von Dungern; in spite of all the newer methods of serodiagnosis, the classical Wassermann reaction, or a method which departs from it only in minor details, is the only one employed at present by reliable serologists.

Recently, the phenomenon of Vernes has been called attention to by Cornwall and Aronson,<sup>1</sup> who describe the method and express the belief that this discovery if confirmed, will revolutionize the diagnosis of syphilis. The reaction consists essentially in mixing certain quantities of patient's serum with pig serum and an organic colloidal sus-



pension prepared from horse heart, incubating at 37.5° C. for one and one-quarter hours and adding sheep cells in 50 per cent saline solution; the tubes are again incubated for 30 minutes and then centrifuged. The pig serum is said in the first stages of the reaction to prevent flocculation which occurs only with syphilitic sera, and the sheep cells are added as an indicator of the total or partial utilization of the antiflocculant power of the pig serum. The result is a series of color tints varying from bright red in normal sera, to a complete absence of color in specific sera, these changes occurring in zones. Although Vernes in 1913, vouched for the specificity of the reaction and made unqualified assertions as to its reliability, no one after him has since confirmed its value. Cornwall and Aronson at the present time have this new method under investigation in the neurologic department of Columbia University and are inclined to regard it favorably, even to the extent of holding out hope that it may, by supplanting the Wassermann reaction, offer a standard method for laboratory diagnosis of syphilis. The reaction is fundamentally a colloidal phenomenon and the colloidal preparation designated by the discoverer as Perethynol, is by far more difficult to prepare than any of the reagents employed in the Wassermann reaction. The interpretation depends on the degree of hemolysis and in this particular introduces the same element of difficulty in reading and recording, as confronts the serologists in the Wassermann test. The reaction is a radical departure from our present serodiagnostic methods and should its value be confirmed, it will serve as a diagnostic adjunct and can no more replace the Wassermann reaction than the Lange colloidal gold reaction in spinal fluid (the great value of which has been everywhere established beyond question) has replaced the Wassermann test in the spinal fluid examination.

It is not exaggerating to say that the quantitative element in the Wassermann reaction is equally as important as in quantitative chemistry, and unfortunately, the application of quantitative methods to the former with equal accuracy is impossible, until we know more about the problem of immunity and immunochemistry. The importance of the quantitative element varies inversely with the volume of reagents and serum employed by the individual worker; yet there are workers who persist in the drop method when minutely and accurately graduated apparatus is so readily obtainable. Fallacious results are

inevitable unless a particular volume decided on is devotedly adhered to in all tubes throughout all titrations; by volume is meant not gross bulk but concentration and degree of activity. It is unfortunate, that many who have written on the subject, particularly along clinical or statistical lines, have failed to describe their technic or have described it too imperfectly to be of value. Ottenberg has made the excellent suggestion that in the future, all workers describe their methods in terms of the original Wassermann volume, simply stating that the actual quantities used were one-half, one-fourth or one-fifth of those given.<sup>2</sup>

The manifold and overwhelming significance of a Wassermann report in its hygienic, economic and social phases, makes it imperative that the clinician have a comprehensive knowledge of the factors that enter into the interpretation of the report. To a certain extent, these factors are not generally applicable, since they vary according to the serological methods employed, so that a knowledge of the particular laboratory consulted, its standards and technic, is essential. The clinician should know that there exists the possibility of obtaining a false negative result where sheep cells are used in the hemolytic system. Of profound importance is a knowledge of the antigens employed, their sensitivity and specificity, the method and length of fixation and the system used to report results. Most important of all, it is the duty of the clinician to know the possibilities of error in the particular laboratory employed. It is well to emphasize here that the work has numerous pitfalls and therefore should be done only by properly trained and skilled workers and the results carefully controlled.

The importance of exercising proper precautions in the collection of the specimen, cannot be too strongly emphasized and is called attention to, in virtue of the fact that it is not possible for the pathologist to obtain every specimen, personally. The slightest trace of acid or alkali or for that matter any chemical substance, renders the reaction unreliable. In a series of 48 placental bloods, 38 or 80 per cent resulted in an anticomplementary reaction. Investigation into the method of collection, revealed the fact that in most instances, the cord was cut after pulsation had ceased, making it necessary to strip the cord into the tube, during which procedure, the specimen must become contaminated with lysol, glove powder and other impurities.

Frequently, the cord was cut with scissors freshly removed from lysol. In the laboratory, the addition of minute traces of lysol to a number of otherwise clearly reacting bloods, rendered the results anticomplementary, and in two instances gave a false positive reaction. The specimen should be collected with material furnished by the laboratory, such needles and glassware being chemically clean and properly neutralized. Blood which has touched the chemically prepared skin must not be allowed to enter the container. In cases where it is not possible to obtain the specimen from a vein, it is best to wash the skin to be punctured with sterile water instead of the usual preparation with iodine and alcohol.

The technic employed in this laboratory is clearly described by Park and Williams in the seventh edition of their book<sup>3</sup> and is the method used by the New York Health Department in their serological laboratories. This technic differs from that of Wassermann's in three respects; (a) In the volume of the test, (b) In the amount of antigen used, and (c) In the method of fixation. All reagents are used in one-tenth the amounts originally used by Wassermann and the test is performed with a constant amount of antigen and varying doses of serum, instead of varying amounts of antigen. The advantages of the small volume method are in the considerable saving of material and in the very small amount (about .2 c.c. of the patient's serum) which is sufficient for the test. Park and Williams have found this method to yield results which are absolutely reliable. The possible error of obtaining false negative reactions with bloods containing natural antisheep amboceptor is eliminated, if the test is read as soon as the control tubes are completely hemolyzed. The use of a constant amount of antigen gives essentially the same results as the use of varying amounts. Fixation, in addition to being carried out in the usual way for one hour in the water-bath, is performed in duplicate series by fixation for four hours in the ice box. Since the velocity of fixation varies directly with the temperature, as does any chemical reaction, the fixation time is proportionately increased with lower temperature and with longer fixation, a firmer and more complete fixation occurs. The objections voiced against the prolonged ice box method of fixation are first, the disadvantage of the prolonged length of time required and the fact that the method frequently yields false positive reactions, since fixation is likely to be nonspecific. In spite



of these objections, it will be pointed out that the four hour ice box fixation does have a definite place in the Wassermann reaction.

The choice of antigen, particularly the use of cholesterin reinforced alcoholic extract, is still a vexed question in spite of the enormous amount of work which has been done on this subject. Practically all workers are agreed that the extracts of syphilitic organs, need no longer be considered in the practical performance of the reaction. At the present time, in spite of the many lipid preparations which have been recommended, practically, there are but three antigens in common use, namely, the simple alcoholic extract of heart muscle, the acetone insoluble fraction after the method of Noguchi, and the cholesterin reinforced alcoholic extract after the suggestion of Sachs, Walker and others. Recently, the question of liver extracts has been revived; Durupt of the Paris Faculty of Medicine,<sup>4</sup> states that liver antigens give about 15 per cent more positive reactions than other antigens and he found that when liver and heart antigens were used parallel, the reaction was always more pronounced with the former in the case of active syphilis. He further assigns to liver antigen a truer biologic significance. During a period of two months, I worked with a liver extract prepared from fetal guinea pig livers, running parallel series with human heart extracts. It was demonstrated that the cholesterinized liver extract can be made to work in much higher dilutions than similarly prepared heart extracts, for example, a dilution of 1 in 200 as compared to 1 in 150, and in the crude form, a dilution of 1 in 40 as compared to 1 in 15 or 20. Although the results were practically identical, except for a somewhat larger number of fixations obtained with cholesterinized liver extract in treated cases, it was observed that as a whole, the liver extracts were definitely less constant in their antigenic properties, necessitating far more frequent titrations and also that they were more likely to become anticomplementary on standing.

A very important element responsible for the growing lack of confidence in the Wassermann reaction is the discredit the test has received from more or less recent reports showing a significant percentage of cases with positive Wassermann reactions and negative autopsy findings and cases with negative Wassermann reactions and positive autopsy findings. Certainly, the marked discrepancy in the postmortem findings of Symmers and Turnbull,<sup>5</sup> throws no light on

this phase of investigation. All investigators who have written on the value of the Wassermann reaction on a basis of autopsy findings, must base their conclusions on results in a routine series which has come to autopsy and, in which, a Wassermann test has been performed in a routine fashion. The great majority of these is composed of patients generally, middle aged or older, who come to the larger institutions with some terminal chronic condition, or possibly younger subjects dying from some acute infection. We all know the relative value of histories obtained from the former class and of the possibility that any number of these have, at some time during life, been knowingly or unknowingly subjected to specific treatment, a procedure which must modify the final anatomic changes. Whereas during life, it is a simple matter to detect superficial and in many instances pathognomonic changes, such as superficial lymphadenopathies, indurative leucoplakia, thickening of the pretibial periosteum or roughening of the anterior border of the tibia, increased consistency or diminished sensitiveness in one or both testicles, ophthalmoscopic signs of chorioretinitis pigmentosa and others, it is far more difficult to detect these and visceral manifestations, years after an initial infection, when time and possibly treatment have masked changes which were once pathognomonic and eventuated in a sclerosis, very often indistinguishable from that resulting from any inflammatory process.

The determination of the condition of the reflexes, the presence or absence of an Argyll Robertson pupil, the sense of coordination, the examination of the eye grounds, all of these are not possible in the autopsy room. It is therefore apparent that the determination of the "clinical specificity" of the Wassermann reaction, in lieu of being based almost entirely on postmortem findings, should depend more on the checking up of serological data with observations on the living patient in all his functions. Certainly, it is far easier to detect pathology in function and the various gross superficial changes already mentioned, as well as certain visceral manifestations, immediately after the performance of the Wassermann reaction, at which time there is in most cases the maximum unmasked physiologic and anatomic pathology, rather than weeks, months or even years, after the Wassermann has been performed and time and treatment have had their effect.

In view of the multiplicity of differences in technic, the unsettled

question of choice of antigen and the fact that the individual element plays so important a rôle in the performance of the reaction, we are really not yet in a position to reach any absolute conclusions regarding specificity. The necessity for standardization is apparent. There is no doubt that the reaction properly performed and accurately controlled, can be made to correspond with almost constant accuracy, even when performed on the same bloods in different laboratories, with different technic. Solomon,<sup>6</sup> in a series of three thousand bloods subjected to the Wassermann test by two independent laboratories, reports that in 93.5 per cent of the cases, there was a complete uniformity in the findings; repetition of the test on the reactions not in accord, brought the percentage of uniform results even higher. Apparently, then, the cause for discrepancies in estimation of clinical value does not rest so much in the exact serological findings, but almost entirely in the fact, that identical results are reported differently by individual workers and hence the underlying cause of differences in interpretation. A personal communication to ten laboratories employing at least two antigens, in this city and in New York, revealed an astonishing difference, in fact, no four laboratories using the same method. Three laboratories use Citron's method of recording results, (four plus, three plus, two plus and one plus) with a statement of the antigens used and the results with each. Three laboratories make no note of the antigens used, simply reporting the test as positive or negative, on the basis of the history obtained from the patient. Two serologists report the findings with crude antigen alone, although they employ cholesterin reinforced extract with every test. In this laboratory it is a matter of routine to report the exact findings with crude and cholesterinized antigen, even though the results be widely divergent; where the findings do not coincide, it is customary to append an explanatory note, as for example, a reaction giving a three or even a four plus with cholesterinized antigen and a plus-minus or negative with crude, may be regarded as negative if clinical manifestations of lues are definitely lacking and the history is negative.

Undoubtedly, no element in the reaction has caused greater confusion in the medical mind, than the divergent systems used by different workers in reporting to the clinician the strength of the reaction. It is apparent that identical serological findings reported by different methods, must give rise to grave differences in interpretation, par-



ticularly among clinicians who are not thoroughly acquainted with the significance of the various antigens. This point is well illustrated by the following occurrence. A physician desiring to have a Wassermann test performed, submitted his blood to me and obtained a report of three plus with cholesterinized antigen and plus-minus with crude extract. In view of a negative history and an entire lack of any clinical evidence of lues, he was told to regard the reaction as "negative." In spite of this, he had the test repeated in another laboratory which reported the test as negative. He was much surprised to see so marked a divergence in the findings. However, a personal communication with the serologist who repeated the test, revealed the fact that he had obtained a four-plus with cholesterin antigen and a plus-minus with crude extract (with entirely different technic), but reported the test negative because it is customary for him to disregard fixation with cholesterin antigen alone, when the case is an untreated one and clinically negative.

In spite of the enormous amount of work which has been done to determine the clinical value of the Wassermann reaction, it is highly probable that conclusive results will not be forthcoming, until the prevailing chaotic multiplicity of methods is replaced by standards, to be determined by a representative official organization of serologists. I would suggest that the very first step, consist in the adoption of a constant method of reporting serological findings, this scheme to be used universally. At the present time, the most desirable appears to be the quantitative method of Citron (one, two, three, and four plus), with a full statement of the findings with both crude and cholesterin antigen; this is the only method that offers information of the progress of cases under treatment. The next and more difficult step would consist in the universal adoption by all recognized laboratories, of a definitely standardized technic. If an individual preferred to work with an original method or preferred other antigens, he would be at liberty to run parallel series with the adopted method. Such a system would promote serological progress, since the results with one's own technic could be compared to the standard and any advantages more readily noted. In this way, any definitely demonstrated improvements in the reaction, if approved by the representative serologists, would be incorporated with or substituted for certain steps in the standard technic. Under a standard system, it

would not be a burden for the clinician to familiarize himself with the features of the test which he ought to know, as well as the possible sources of error, a practical impossibility under prevailing serological conditions. Furthermore, the findings in checking up by clinicians and pathologists of serological data with clinical and anatomical observations, would be infinitely more uniform.

In an attempt to compare the specificity and sensitivity of crude and cholesterin reinforced extract, in conjunction with the four hour ice box fixation method as well as the one hour water-bath fixation, a series of tests was conducted on the bloods of 580 cases. Each serum was tested with crude extract of human heart and cholesterin reinforced extract and subjected to both the one hour water-bath and four-hour ice box methods of fixation. The technic employed was the one tenth volume method described by Park and Williams, and outlined in Table I. The preparation of reagents and their standardization is described in the seventh edition of their book "Pathogenic Microorganisms."<sup>3</sup>

TABLE I  
TEST OF SERUM FOR DIAGNOSIS OF SYPHILIS

NUMBER OF TUBE	PATIENT'S SERUM C.C.	ANTIGEN IN STANDARD DILUTION C.C.	TEN PER CENT COMPLEMENT C.C.	0.85 PER CENT SALINE C.C.	SENSITIZED ERYTHROCYTE SUSPENSION C.C.
1.	.02	.1	.1	.1	.2
2.	.01	.1	.1	.1	.2
3.	.04	.0	.1	.2	.2
4.	.02	.0	.1	.2	.2
5.	.0	.2	.1	.0	.2
6.	.0	.1	.1	.1	.2

- Serum controls
1. Duplicate diagnostic test to detect error in technic.
  2. Test for natural antisheep amboceptor to avoid false negatives.
  3. Test for anticomplementary unit.
  4. Test for lytic action upon cells alone.
- Antigen controls
1. For specificity of antigen. { Diagnostic test with known positive and known negative serum.
  2. Test for anticomplementary unit.
  3. Test for fixation unit.
  4. Test for lytic action with complement when no amboceptor is used.
- Control tests of each serum and of the antigen are made as in the classical Wassermann.

In each case, a complete history was taken and the patient subjected to a thorough physical examination, including special examinations, ophthalmological and neurological when indicated. The tests

on the spinal fluids were carried out with the identical technic, except that five times as much spinal fluid as serum was used. A tabulation of the results of the serological findings is shown in Table II.

TABLE II  
TABULATION OF SEROLOGICAL FINDINGS WITH BOTH ANTIGENS AND BOTH METHODS OF FIXATION

	CHOL. ANTIGEN 4 HRS. ICE BOX	CHOL. ANTIGEN 1 HR. WATER-BATH	CRUDE EXTRACT 4 HRS. ICE BOX	CRUDE EXTRACT 1 HR. WATER-BATH
Four Plus	139	118	108	93
Three Plus	17	18	25	5
Two Plus	7	10	18	13
One Plus	5	8	10	1
Plus-Minus	16	20	9	6
Negative	396	406	410	462

A glance at the foregoing table reveals the fact that by far the greatest number of positives is obtained by the four hour ice box method of fixation with the cholesterinized antigen, this method yielding 139, or 23.9 per cent, four plus reactions as compared with 118, or 20.3 per cent, with cholesterinized antigen water-bath, 108, or 18.6 per cent, with crude extract in the ice box and 93, or 16 per cent, with crude extract in the water-bath. Although it is an undisputed fact that the cholesterin reinforced antigens are by far more sensitive than the crude alcoholic extract, it is interesting to note that in this series, the crude alcoholic extract fixed for four hours in the ice box is almost as sensitive as the cholesterin reinforced antigen, fixed for one hour in the water-bath at 37° C. The crude alcoholic extract fixed for four hours in the ice box yielded 100 four plus reactions as compared to 93 obtained with the identical extract on the same sera when fixed for one hour in the water-bath.

The increased sensitivity of the prolonged ice box fixation method is emphasized by Burdick<sup>7</sup> who states that the advantages over the short water-bath period are decided. In a studied series, he obtained a much higher percentage of positives by the prolonged primary ice box incubation method, especially in second stage treated cases and third stage untreated cases. While these conclusions are substantiated by the findings in our series, it will be pointed out that the prolonged ice box fixation method involves a nonspecific element and that its advantages are dependent on the antigen used and the clinical picture of the case under examination.



While the foregoing determinations of sensitivity are based entirely on observation of exact findings, any determination or estimation of specificity, must be a difficult matter in view of the fact that here, there enters a personal factor and much depends upon the individual's powers of observation and interpretation of clinical findings. With this fact in mind we can proceed to make the following observations.

Of the 85 four plus reactions obtained with crude extract by water-bath fixation, every case presented unmistakable clinical evidence of lues, showing therefore an absolute specificity, there being no false positive reactions. Two of these cases having positive histories and showing, respectively, hepatic and osseous manifestations which yielded readily to antiluetic treatment, reacted negatively to cholesterin reinforced antigen, in spite of the four plus reaction with crude extract. Identical findings were obtained by repeating the tests with a second sample of blood. Such a reaction is unusual and further emphasizes the specificity of crude antigen. The cholesterinized antigen fixed for 4 hours in the ice box, yielded on the same sera, 139 four plus reactions; if we subtract from this number the 85 clinically specific cases, 35 treated cases which although weakly positive or negative to crude extract were at one time completely fixed with both antigens, 8 cases of neurosyphilis which although having blood reactions negative to crude, yielded a four plus reaction to both antigens with their spinal fluids, and 2 cases from whom the blood had been taken within 36 hours following ether anesthesia, a total of 130, there remain 9 cases in whom no clinical evidence of lues was demonstrable and in whom the following clinical diagnoses were made: Vincent's angina (one), carcinoma of stomach with hepatic metastasis (one), fracture of long bones (two), lobar pneumonia (two), inguinal hernia (one), and two perfectly healthy individuals who themselves desired the test and gave negative histories. All of these 9 cases reacted negatively with crude extract. Here then, we have 1.55 per cent false positive reactions with cholesterinized antigen, a finding which is not in accord with recent opinions that in this climate, fixation with cholesterinized antigen alone, in a test properly controlled, is always diagnostic of syphilis. Ten serologists with whom I have personally communicated, agree that a positive reaction with cholesterin antigen alone, in the

absence of a positive history and clinical evidence of lues, should be given absolutely no specific significance.

However we can assign to the cholesterinized antigen a specific sensitivity under the following circumstances; (A) cases undergoing treatment, (B) congenital syphilis, (C) neurosyphilis.

The great value of cholesterinized antigen in following up treated cases can be readily seen in the fact that of 35 clinically specific cases, which at the outset gave a four plus reaction to both crude and cholesterin antigens and after a course of 6 salvarsans and mercurialization yielded completely negative reactions with crude extract, each of the 35, continued to show a four plus with cholesterinized antigen fixed for four hours in the ice box, while only 28 of them gave a four plus reaction with the same cholesterinized antigen fixed for one hour in the water-bath, the remaining 7 yielding weakly positive reactions. The specific sensitivity in congenital syphilis may be seen in the fact that 12 cases of undoubted congenital syphilis giving weakly positive or negative reactions with crude extract, gave in 10 cases a four plus and in 2 cases a three plus with cholesterinized antigen. It is interesting to note that 8 of these cases occurred in one family, to which attention was attracted by the death of a 17 year old boy, dying with the symptoms and signs of empyema and revealing at autopsy multiple gummata of the liver with abscess formation and extension into the chest through the diaphragm. While the father gave a four plus reaction with both antigens, the remaining 6 children, 4 of whom showed definite clinical evidence of congenital lues, yielded the following serological findings; 1 gave a four plus with cholesterin and two plus with crude extract; 2 gave a three plus with cholesterin and plus-minus with crude; 1 a three plus with cholesterin and negative with crude.

It appears that we can assign a specific sensitivity to cholesterin antigen in some cases of neurosyphilis. In a series of 18 spinal fluids all of which gave a four plus reaction with both antigens, the blood Wassermann was entirely negative in 10. Two cases gave a four plus blood Wassermann reaction; these were the only cases in the series in which nervous system involvement manifested itself within two years from the initial lesion; all the others were cases of late neurosyphilis. Of the remaining six cases, all gave a positive reaction to cholesterin

varying from two to four plus, two reacted weakly with crude extract, while four were entirely negative with crude antigen. In this connection, it is important to emphasize the value of lumbar puncture in all cases where syphilis is suspected and the blood reacts negatively or is positive only with cholesterin antigen. It is strongly advisable to perform a lumbar puncture in all cases which have been thoroughly treated, before pronouncing a prognosis. The blood Wassermann is never a criterion for the presence or absence of nervous system involvement and the syphilitic whose blood has been rendered negative by active treatment, has no guarantee that he will not in future years, be visited by neurologic complications. In our series, four cases with osseous involvement, (one a spontaneous fracture of the neck of the femur, one an arthritis of the knee joint and two cases of tibial osteomyelitis) each gave a negative blood Wassermann reaction; in spite of this, all gave a four plus spinal fluid reaction to both antigens, showing in addition, a pleocytosis varying between 45 and 180 cells and a colloidal gold curve in two cases luetic and in the other two, parietic. All four cases responded remarkably to specific treatment. In my experience, the colloidal gold reaction has never given a normal curve where the spinal fluid Wassermann was at all positive and in some instances, has given a luetic curve when the spinal Wassermann has been negative. The conception on the part of many clinicians, that lumbar puncture is a harmful procedure, is largely responsible for the fact that so few lumbar punctures are done in the routine treatment of syphilitics. The procedure is very simple and practically devoid of objectionable complications, three cubic centimeters of fluid being sufficient for the performance of the routine examination, Wassermann and colloidal gold reactions. Every neurologist has met cases which present a negative blood Wassermann with unmistakable clinical evidence of neurosyphilis; some of these give a positive history and have taken treatment some years before, some have never been treated, while others are cases of congenital syphilis. Recently, Kingery<sup>8</sup> who has made a study of the spinal fluid in congenital syphilis, emphasizes the importance of routine lumbar puncture, not only as a diagnostic procedure but also on account of its influence on prognosis.



## SUMMARY

1. In spite of the multitude of modifications and newer methods for the serodiagnosis of syphilis, including the phenomenon of Vernes recently revived by Cornwall and Aronson, the classical Wassermann reaction or a technic which departs from it only in minor details, stands today as the only reliable laboratory test for syphilis.

2. The reasons for the growing lack of confidence in the Wassermann reaction on the part of clinicians are presented, together with a discussion of the causes for discrepancies in estimation of clinical value.

3. Attention is called to some of the pitfalls of the reaction and the observation of the clinician is directed to the features of the reaction which he ought to know, in order to be able to more properly interpret serological findings. Thus, the clinician would be in a position, as he has a right to be, to demand from the serologist not merely a report of positive or negative, but a report of the antigens used in the test with the methods of fixation and himself interpret the serological findings on a basis of clinical manifestations.

4. The great need for standardization with the benefits to be derived therefrom is called attention to, and some suggestions are offered to bring about uniformity.

5. A series of 580 reactions performed with crude and cholesterinized extract each with two methods of fixation, namely, the one hour incubator and four hour ice box methods, is analyzed with the following conclusions;

A. A positive reaction with cholesterinized antigen alone should be given no specific significance in untreated cases presenting no clinical manifestations of lues and giving a negative history.

B. The four hour ice box method of fixation, while increasing the sensitivity of the cholesterin antigen as compared with the one hour fixation in the water-bath, magnifies the nonspecificity, except in treated cases, congenital syphilis and in some cases of neurosyphilis, where it has a decided advantage. On the other hand, with the crude extract, the four hour ice box method of fixation while increasing its sensitivity, does not impair, but rather augments the specificity.

C. The cholesterinized antigens possess a specific sensitivity exceed-

ing that of crude in all cases of syphilis under treatment, congenital syphilis, and in some cases of neurosyphilis.

6. The great value and importance of lumbar puncture in all cases of syphilis is emphasized. A spinal fluid examination, including cell count, globulin estimation, colloidal gold and Wassermann reactions is imperative before a prognosis in any case can be given, in spite of the fact that treatment has produced a Wassermann negative blood.

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# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

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WM. H. DEADERICK, M.D., EDITOR

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## **Syphilis and Feeble-mindedness in the Alabama State Industrial Schools.—**

Thomas H. Haines, Jackson, Miss., and W. D. Partlow, Tuskaloosa, Alabama.  
Ohio State Medical Journal, 1920, vol. xvi, p. 515.

Of 672 white girls, white boys and negro boys in Alabama Industrial Schools, 118 are feeble-minded. These are institutional cases, needing life-long care to prevent crime, immorality and propagation of their kind. Sixty-three others are adjudged as having borderline intelligence. Many of these may turn out to be institutional cases. Eighteen others are found to be constitutional inferiors or psychopaths, and therefore in need of custody, or medical treatment, and not reformable. About 25 per cent of these populations is, therefore, improperly placed in these educational and reformatory institutions. It is not likely they can be educated or rehabilitated socially on account of mental condition. Of the serum specimens from 103 white boys, only one yielded a positive Wassermann and two Cholesterin positives. Of 147 serum specimens from negro boys, 31 yielded positive Wassermanns; 13 of these were of the 59 adjudged feeble-minded; 3 of the 46 adjudged borderline; 2 of the 8 constitutional inferiors; leaving 13 positive Wassermanns amongst the 34 judged as of normal mentality after individual mental examinations. This gives us no evidence of a high rate of incidence of syphilis amongst the mentally inferior. Hutchinson teeth as a sign of congenital syphilis are very rare among these boys. Anomalies of reflexes, such as commonly indicate syphilitic invasion of the nervous system, are still rarer; only 3 cases reported, 2 of these feeble-minded.

## **The Effects of Syphilis on the Families of Syphilitics Seen in Late Stages.—**

Harry C. Solomon and Maida H. Solomon, Boston. Social Hygiene, 1920, vol. vi, p. 469.

The families of syphilitic patients admitted to the Psychopathic Hospital have been examined as a routine procedure. The patients are all in the late stage of the disease and are divided into three groups: (1) general paresis, (2) cerebrospinal syphilis, and (3) late syphilis without involvement of the



nervous system. This division is made to determine whether the familial problem is different in cases of central nervous system involvement from those in which the central nervous system escapes. The families of 555 syphilitic patients were examined and the following findings were obtained: The family of the late syphilitic abounds with evidence of syphilitic damage. At least one-fifth of the families of syphilitics have one or more syphilitic members in addition to the original patient. Between one-third and one-fourth of the families of syphilitics have never given birth to a living child. This is much larger than the percentage obtained from the study of a large group of New England families taken at random which shows that only one-tenth were childless. More than one-third of the families of syphilitics have accidents to pregnancies; namely, abortions, miscarriages, or stillbirths. The birth-rate in syphilitic families is 2.05 per family; whereas the birth-rate in the New England families mentioned above is 3.8 per family, or almost twice as great. Two-thirds of the families show defects as to children (sterility, accidents to pregnancies, and syphilitic children). Only one-third of the families show no defect as to children or Wassermann reaction in spouse. About one-fifth of the individuals examined show a positive Wassermann reaction; more of these are spouses than children. Between one-fourth and one-third of the spouses examined show syphilitic involvement. Between one in twelve and one in six of the children examined show syphilitic involvement. One-fifth of all children born alive in syphilitic families were dead at the time the families were examined. This does not differ materially from the general average in the community. One-fifth of the pregnancies are abortions, miscarriages, or stillbirths, compared with less than one-tenth of the pregnancies in nonsyphilitic families. The average pregnancies per family are 2.58, compared with 3.88, 4.43, and 5.51 in nonsyphilitic families.

**Experimental Syphilis in the Rabbit. Affections of the Skin and Appendages.—**

Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1920, vol. xxxii, p. 445.

From the study of a large series of rabbits with outspoken manifestations of generalized syphilis, lesions of the skin and appendages were found to constitute one of the largest and most varied groups of such affections. The conditions noted consisted of alopecia, onychia and paronychia, and lesions of the skin proper. It was found to be a matter of some difficulty to make a positive diagnosis of syphilitic alopecia, but there were three and possibly four conditions which appeared to be attributable to such an affection. The first of these took the form of a general or local roughening of the coat with falling of the hair which produced the typical moth-eaten appearance associated with syphilitic alopecia in the human subject. A second form of alopecia was essentially an abnormal looseness of the hair which permitted large areas of the body to be completely denuded. The third type of alopecia was associated with definite skin changes, and the hair was readily removable together with an adherent mass of epithelial scales. Panoychia was comparatively rare

but was readily recognized by a characteristic infiltration and exfoliation of the skin about the base of the nails. The incidence of onychia is uncertain. Late in the course of the investigation it was found that alterations in the nails which were not entirely characteristic in themselves might occur in consequence of a syphilitic involvement of the nail beds which could not be detected by ordinary methods of examination. The cases which were recognized as syphilitic were those which showed an associated paronychia. Lesions of the skin were found to be one of the most frequent manifestations of a generalized infection in the rabbit. These lesions were divided into three classes: first, granulomatous lesions, second, infiltrations, and third, erythematata. The granulomatata were lesions of a fleshy character which tended to grow to a very large size and presented all the characteristics of circumscribed primary lesions of the scrotum. The conditions described as cutaneous infiltrations included two general types of lesions, one a flattened and rather diffuse process, the other an elevated and sharply circumscribed papule. As a class, these lesions were very prone to secondary alterations and in this way gave rise to a great variety of conditions which in general resembled the diffuse primary lesions of the scrotum and the papular lesions resulting from local dissemination. A third type of lesion resembling the macular erythematata of man was observed in a small number of animals, and while no definite proof of the specific origin of these lesions was obtained, the evidence available was strongly suggestive. In addition, several other cutaneous affections were noted which have not as yet been thoroughly investigated. It is suggested, however, that these processes may bear some relation to infection with *Treponema pallidum*.

**Experimental Syphilis in the Rabbit. Clinical Aspects of Cutaneous Syphilis.—**

Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1920, vol. xxxii, p. 473.

From the study of a large number of rabbits with generalized cutaneous syphilis following local inoculation with *Treponema pallidum*, lesions were found most often about the hind feet and legs, the head, the front feet and legs, and the tail. There was further evidence of a selective distribution of cutaneous lesions in the fact that, on a given part of the body, the lesions were usually confined to a few restricted areas. About the head, they occurred almost exclusively on the sides and bridge of the nose, the lids, the brows, the lips, and the base and free portions of the ears. On the front feet and legs, the seat of predilection was the extensor and lateral surfaces of the forearm, the carpus, and the feet, while on the posterior extremities they were situated upon the dorsum and lateral surfaces of the feet and ankles from the level of the tendo achillis to the base of the fifth toe. The positions of greatest frequency were the region of the tarsus and external malleolus, the base of the fifth metatarsal, the lateral and posterior surfaces of the heel and tendo achillis, and the base of the fifth toe. In many instances, the positions of predilection were exposed positions or areas of skin covering bony or tendinous prominences. It was also found that the character of the lesions differed some-

what in the various locations. The lesions of the head were mostly small circumscribed papules or processes of diffuse infiltration; on the forearms and feet, affections of this type were about equally divided with larger granulomatous masses of a chancre-like character, while on the hind feet and legs, granulomatous lesions were far more numerous than those of any other type and frequently reached a very large size. The cutaneous eruption usually consisted of only a few lesions confined to some one part of the body, but occasionally they were more numerous and more widely distributed. In this connection, it was noted that when multiple lesions appeared in a given area at about the same time, the growth of most of them was abortive, and, as a rule, only one or two developed to any considerable size. Especial emphasis was placed upon the phenomenon of inhibition as a factor of fundamental importance in the experimental infection. From clinical observation, it was found that, as a rule, the first cutaneous eruption occurred at from 2 to 4 months after inoculation but might occur either earlier or later, depending upon the circumstances in the individual case. The earliest eruptions appeared 3 weeks after inoculation and the latest 2 years and 8 months, but, as a rule, the time between inoculation and the appearance of the first eruption did not exceed 4 to 6 months. Successive crops of cutaneous lesions appeared in a number of animals usually within the first 6 months after inoculation. In a few instances, however, there were repeated eruptions extending over a period of 2 years or more, the longest recorded period being 3 years and 7 months. The duration of individual lesions was found to be extremely variable, ranging from a few days in the case of a macular erythema to more than 2 years in the case of a few granulomatous lesions. The average duration of the lesions appeared to vary somewhat with the nature of the lesion but on the whole was not more than 2 to 4 months. No limits could be fixed, however, for the duration of an active skin infection as a whole. Again it was found that the cutaneous infection tended to pursue a periodic or relapsing course. This was seen in the mode of growth and resolution of individual lesions, the occurrence of successive periods of eruption, and the recurrence of completely healed lesions, all of which was interpreted as evidence of the essential relapsing nature of syphilitic infections.

**Experimental Syphilis in the Rabbit. Syphilitic Affections of the Mucous Membranes and Mucocutaneous Borders.**—Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1920, vol. xxxii, p. 497.

In a series of more than 200 rabbits in which generalized lesions were observed following local inoculation with *Treponema pallidum*, there were a number of animals in which characteristic lesions were noted upon mucous membranes or along mucocutaneous borders. These lesions were distributed with about equal frequency between the nose or nasolacrimal system and the eyelids on the one hand, and the genital and anal regions on the other. The lips and buccal mucosa appeared to be less subject to localized infections unless the papillomatous growths noted on the lips and under side of the tongue



should prove to be in some way connected with such an infection. In many instances, the local reaction was initiated by an acute inflammatory process, and in the case of nasal and genital infections, a definite exudate formed. The succeeding stages of the reaction consisted in an infiltration of the parts involved, together with a variable degree of proliferation of fixed tissue cells, leading eventually to necrosis and ulceration. The resulting lesions differed according to their location and the character of the reaction in the individual case. Localized infections of the nose occurred in several forms, first, as a rather diffuse affection of the nasal mucosa characterized by the presence of a mucopurulent exudate, second, as a more or less circumscribed process of infiltration with an especial predilection for the region of the anterior nares, and third, as a granulomatous process involving the alæ in particular. Involvement of the nasal mucosa was very commonly associated with lacrimal overflow and with some degree of conjunctivitis. The lesions of the eyelids were usually small, elevated papules or lesions of an ulcerative character some of which were surrounded by a zone of infiltration. In exceptional instances, large granulomatous lesions occurred along the margins of the lower lids. Infection of the penis and sheath gave rise to conditions analogous to those of the nose. In one group of animals, there was a diffuse affection characterized by redness and swelling of the parts with a mucopurulent exudate, in another there were circumscribed or diffuse infiltrations, while in a third the lesions formed were indurated granulomatous masses. Secondary necrosis with erosion or ulceration was a common feature of all these conditions. Localized infections in the region of the anus differed from those in other localities chiefly in the absence of an exudative group of affections and in the frequency with which lesions of a papillomatous type occurred. Lesions of mucous membranes and mucocutaneous borders developed at periods of time varying from a few weeks to several months after inoculation. Most of them were rather enduring and in several instances persisted in an active condition for considerably more than a year.

**A Note on the Dissemination of *Spirochaeta Pallida* from the Primary Focus of Infection.**—Wade H. Brown and Louise Pearce, New York. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 470.

While the conditions of these experiments are not entirely analogous to those that obtain in cases of human infection, the general course of events is undoubtedly much the same in the two cases. It would appear, therefore, that, for practical purposes, there is probably no appreciable time during which a syphilitic infection can be regarded as confined to the focus of entry but that, immediately infection takes place, the spirochetes begin to multiply and invade the surrounding tissues, gaining access to both the lymphatics and the blood stream, and are widely distributed over the body even before an initial lesion can be detected. The early appearance of a distinctive lesion at the site of infection and the lapse of time required for the development of generalized lesions are to be viewed more as a result of a sequence in localization and con-

centration of spirochetes at given points than as indications of the time required for their dissemination.

**Syphilitic Infection of the Central Nervous System of the Rabbit.**—Wade H. Brown and Louise Pearce, New York. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 635.

This series of experiments, although too limited to warrant any broad generalizations in regard to syphilitic infection of the central nervous system, is sufficient to show that such infections may be produced in the rabbit by an ordinary testicular inoculation of well adapted strains of *Spirochaeta pallida*, and that spirochetes may invade the central nervous system at a very early period of the infection. How often this occurs is impossible to say since the methods used are subject to obvious limitations both as regards the type of infection which may be demonstrated in this way and the activity of the infection at the time the examination is made. From this small series of experiments, it would appear, however, that invasion of the central nervous system by *Spirocheta pallida* and the development of localized lesions are subject to the operation of the same set of conditions as are concerned in the occurrence of other manifestations of a generalized infection, and that by taking advantage of these conditions, it should be possible to favor this form of infection so as to increase both the incidence and severity of central nervous system involvement.

**Gummatous Epididymitis and Gummatous Osteoperiostitis of the Humerus.**—Lewellys F. Barker and James Alto Ward, Baltimore, Md. *Southern Medical Journal*, 1920, vol. xiii, p. 794.

Syphilitic epididymitis, though a rare condition, may be met with in either hereditary or acquired lues, and in either the secondary or the tertiary stage of the disease. The globus major is most often involved, the lesion appearing as a firm nodular mass, which forms a cap for the end of the testicle, the latter resting, as it were, in a clam-shell. The French describe the epididymis appearing as a "helmet crest" for the testis. The absence of pain is a characteristic feature. The epididymis and the testis have several times been unnecessarily removed in syphilitic epididymitis because of a wrong diagnosis, the condition having been mistaken either for tuberculosis or for neoplasm. The importance of a general diagnostic survey for the purpose of differentiating between the different forms of enlargement of the epididymis and testis is obvious. Gummatous epididymitis clears up quickly under intensive anti-luetic treatment.

**Pulmonary Syphilis.**—J. H. Gibbes, Columbia, S. C. *Southern Medical Journal*, 1920, vol. xiii, p. 788.

A chronic pulmonary disease, physically indistinguishable from the common types of chronic pneumonitis and producing a symptomatic picture similar to

that of pulmonary tuberculosis, is not infrequently associated with a positive Wassermann reaction, and the favorable change in general and local conditions following antisyphilitic treatment is so striking as to lead one to the opinion that the syphilitic process is at least in part responsible for the pulmonary pathology. A Wassermann reaction should be a routine in the investigation of all chronic pulmonary diseases, even though the tubercle bacillus or other organisms be found in the sputum.

**Abdominal Syphilis.**—J. Q. Chambers, Kansas City, Mo. *Journal of the Missouri State Medical Association*, 1920, vol. xvii, p. 415.

The author feels that he has shown in this presentation of cases that syphilis plays a very much more important rôle in gastrointestinal pathology than is usually supposed. When one realizes that carcinoma or ulcer of the stomach, various functional or organic dyspepsias may be absolutely duplicated by syphilis of the stomach, while the parasymphilitic tabes may present the most variable gastrointestinal syndromes—here violent epigastric pain, suggesting perforating ulcer or gallstone colic, here intractable nausea and vomiting, here colonic crises which almost duplicate in symptomatology either acute appendicitis or acute enterocolitis, while in other cases periodic attacks of the most profound diarrhea may be met with—it should make us realize that we should always be on the alert for manifestations of this disease either in the past history or in the complete physical examination of the patient. The author feels sure that if such possibilities are thought of, if the history is taken carefully, if the physical examination is complete, with, of course, careful studying of the blood, or even of spinal fluid if indicated, an increasing number of gastrointestinal lesions regarded as due to other causes will, in reality, be shown to be syphilitic in origin.

**Syphiloma Vulvæ.**—Arthur Stein, New York. *Surgery, Gynecology and Obstetrics*, 1920, vol. xxxi, p. 227.

In conformity with modern knowledge and in the interest of a better understanding of the disease, all misleading names such as esthiomene or lupus vulvæ should be exterminated from the literature. Syphiloma vulvæ correctly designates the disease as a manifestation of tertiary lues. A positive Wassermann test is not essential in view of the long standing character of the specific infection in the majority of the cases. The treatment under all circumstances should consist of (1) operative removal of all tumors, hypertrophied tissues and ulcers, followed in the same session by (2) energetic cauterization and combined with (3) intensive antisyphilitic medication.

**The Urine in Syphilis.**—Joseph Victor Klauder and John A. Kolmer, Philadelphia. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 102.

The urine was examined in forty-three cases of untreated primary syphilis, the duration of which was from a few days up to the time of cutaneous mani-



festations. Urinary abnormalities were present in three cases. The urine was examined in forty-six cases of untreated secondary syphilis. Urinary abnormalities were present in four cases. The positive cases all showed albumin and granular casts, except two in which casts were absent. In two cases, red blood cells were present. The albumin consisted of a trace, except that in two of the secondary cases a light cloud was present with many granular casts, and in one red blood cells. The urinary abnormalities disappeared after treatment with arsphenamine and mercury. The urinary abnormalities in secondary syphilis are regarded as due in all probability to an invasion of the kidney by *Spirocheta pallida* rather than due to syphilotoxins which is the explanation usually given. The clear blood serum and the urine, from the same patient, were mixed for the presence of precipitin or precipitogens in serum or urine. The serums and urine of twenty acute untreated secondary cases were tested in this manner. The results were negative in all. Either the antibody is absent in the serum, or the antigen from the urine or both may be absent, as indicated by the results. Clinical and experimental observations show that mercury is considerably more nephrotropic than arsphenamine or neocarsphenamine. In the conjoined intensive treatment of mercury and the arsenicals, the nephrotropic action of mercury may retard the elimination of arsenic and in this way cause untoward effects of arsenic. In view of this possibility, conjoined intensive treatment with mercury and the arsenical preparations is not advised. The Wassermann reaction was performed with the urine of sixty patients with syphilis in the different stages of the disease, many presenting acute symptoms and being untreated. Every patient yielded a positive blood Wassermann reaction, the majority of reactions being strongly positive with three different antigens. Of the sixty cases, the urines in but two yielded positive reactions. Complement-fixation tests with urine are exceedingly liable to yield falsely positive results, owing to the highly anticomplementary activity of the urine. Anticomplementary activity varies with individual specimens. It is greater in old specimens than in fresh ones. Heating in a water-bath at 56° C. for thirty minutes removes only a slight amount of the anticomplementary substances. Falsely positive results with urine are particularly likely if the amount used in the main tests is just under the anticomplementary unit. Under these conditions the control may show complete hemolysis but the antigen tube slight inhibition of hemolysis, which may be interpreted as weakly positive fixation due to the presence of syphilis antibody. Similar results may occur with the urine of healthy nonsyphilitic persons, owing to the summation of the anticomplementary activities of antigen and urine in the antigen tube. In performing the Wassermann reaction with urine, each specimen unheated was titrated for its anticomplementary unit and one-half this amount used. Two methods were used: The first employed 1 c.c. of 1:20 guinea-pig complement in an antishoop hemolytic system, and three antigens including a cholesterolized alcoholic extract of syphilitic liver and an extract of acetone-insoluble lipoids. Primary incubation was conducted in a water-bath for one hour, the technic being that of our regular Wassermann test. A number of

specimens were also tested with a technic employing two units of complement and a primary incubation of eighteen hours at from 6° to 8° C. *Spirochete pallida* may be found in the urine of syphilitics in the acute stage of the disease. There is no characteristic feature in the urine of paroxysmal hemoglobinuria of syphilitic origin which serves to differentiate it from the same condition due to other causes. Results with urinary tests for syphilis were of no value as a means to the diagnosis of syphilis.

**Pseudochylous Ascites in a Case of Syphilitic Nephritis.**—E. L. Tuohy, Duluth, Minn. *Annals of Medicine*, 1920, vol. 1, p. 61.

This case is put on record primarily on account of the character of the ascitic fluid. Finding such in the presence of a nephritis, from the cases previously recorded, as well as this one, one should have in mind the possibility of syphilis. The particular features which should be emphasized are: 1. In the urine the extraordinary number of tube casts found and the high content of albumin. 2. The unusually high blood count. 3. The absence of cardiac hypertrophy or increase in blood-pressure. 4. The finding of low blood sugar and creatinin and a fair phenolsulphonephthalein output usually suggestive of a fair prognosis. 5. Picture otherwise of a "wet nephritis." 6. Finding of pseudochylous transudate. 7. The association of syphilis. 8. The apparent inflammatory reaction, intra-abdominal, during the last few hours of his life could have been a hematogenous infection. In the presence of ascitic fluid one would not expect the ordinary local reactions. It seemed to be simply a terminal condition.

**Juvenile Tabes.**—H. L. Parker, Rochester, Minn. *Archives of Neurology and Psychiatry*, 1921, vol. v, p. 121.

Juvenile tabes is now a well-recognized entity, and with our increased facility of diagnosis, more and more cases are being recognized and reported. The features of the disease that the author has attempted to show may be briefly summarized: The insidious onset, the lengthy and even latent course of the disease, during which time no subjective complaint may be made, are in contrast to the frequent optic atrophy and total blindness that may also occur. The frequency of incontinence of urine, the relative rarity of such striking phenomena as ataxia, girdle sensations and lightning pain, and finally the frequent parietic termination, are features that stamp juvenile tabes with a distinctive mark and distinguish it from the adult type.

**The Clinical Approach to Syphilis, with Suggestions for Its Revival and Development.**—John H. Stokes, Rochester, Minn. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 473.

The author has tried to voice his belief that the revival of clinical syphilology calls for a new type of syphilographer, synthetic rather than analytic in temperament, whose qualities as an inspirer of men, a cooperator, interpreter

and coordinator, will outrank his merely technical expertness in the minutiae of syphilologic diagnosis. Such a syphilographer will direct in his field the efforts of a highly complex diagnostic organization rather than perform a few special tests. He will become expert in the appraisal of the relative significance of a variety of structural and functional investigations which he does not himself necessarily perform. He will endeavor to give concreteness to the intuitive and he will find in highly developed and systematized records that mastery of data which his synthetic powers require for the attainment of a new type of exactitude and conclusiveness in clinical research.

**Diagnosis and Treatment of Early Syphilis.**—William S. Robertson, Charleston, W. Va. *West Virginia Medical Journal*, 1920, vol. xv, p. 164.

The points in dealing with early syphilis upon which particular stress are to be laid are as follows: (1) A positive diagnosis of syphilis can be made with the dark field before the infection is generalized. (2) The prognosis is immeasurably improved if the treatment is begun before the system is swarming with the treponema. (3) Repeated examinations must be made both of blood and spinal fluid to determine, in the absence of clinical symptoms, the necessity for additional treatment. (4) Only when the findings of the blood and spinal fluid are repeatedly negative and the case is clinically free of evidences of the disease, are we justified in discharging the patient as cured.

**Second Improved Method for the Demonstration of Spirocheta Pallida in the Tissues.**—Aldred Scott Warthin and Allen C. Starry, Ann Arbor, Mich. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 234.

The authors regard this method as by far the best one yet devised for the demonstration of spirochetes in tissues. The organisms are dark reddish brown to jet black against a very light brown. With experience it can be so manipulated that only the spirochetes and the nuclei of the tissue are stained, so that a beautiful contrast for demonstration purposes or photomicrographic work is obtained. Further, the rapidity of the method as compared to all other methods for spirochetes in tissue, and its applicability to single sections make it the most practical method for diagnostic work yet devised.

**Dissemination of Spirochete Pallida in Experimental Syphilis.**—Frederick Eberson, St. Louis. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 111.

*Spirochete pallida* have been isolated from the blood stream of experimentally infected rabbits, seven, ten and thirty days after intratesticular inoculation, at times corresponding to twenty-six, twenty-three and three days prior to the appearance of any initial lesion. The regional lymph glands of rabbits have been found to contain active virulent *Spirochete pallida* seven days after inoculation of the rabbit's testicle and twenty-six days before any primary lesion had appeared. The spleen has been shown to contain *Spirochete pal-*



lida more than two months after the inoculated testicle had healed entirely and has been found free from spirochetes by repeated puncture and direct inoculation of the excised testicle into other rabbits. For confirmation of experimental work and for the diagnosis of suspicious syphilitic material which cannot be studied microscopically, it appears that the method suggested by these studies might be employed to advantage. With early invasion of the lymph glands and blood stream established definitely during the incubation period of syphilis in animals, the theory of a life cycle of *Spirochete pallida* is weakened considerably. The absence of organisms, as judged solely by microscopic findings, is not convincing proof that a change of form has taken place within the animal body. That *Spirochete pallida* is found unaltered both in morphology and in virulence in the blood and glands seems sufficient to render the theory untenable.

**The Wassermann Test and Its Limitations in Diagnosis and Treatment.**—G. L. Rohdenburg, A. L. Garbat, Leo Spiegel and P. J. Manheims, New York. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 14.

The Wassermann test is not infallible and its value is greatest when its limitations are clearly comprehended. Some of these limitations are dependent on technical details with which the clinician must familiarize himself until the time arrives when all serologists agree on a standard technic. Other limitations are dependent on the biologic processes involved. Accepting the test as diagnostic in the vast majority of cases, it also serves as an indication of the success of treatment. The data presented in this report emphasize that the earlier treatment is instituted and the more vigorous the early treatment is, the greater the likelihood of obtaining a serologic cure.

**Complement vs. Amboceptor Titrations in the Wassermann Test.**—R. L. Kahn, Lansing, Michigan. *Journal of Laboratory and Clinical Medicine*, 1920, vol. vi, p. 153.

The time of incubation of amboceptor and complement titrations and the time of final incubation before reading the tests, should be the same in any given procedure; the standardization of this incubation period of 15 minutes, is highly desirable. The daily titration of both complement and amboceptor in the Wassermann test, is necessary to a properly balanced hemolytic system.

**Prolonged Ice Box Versus Short Water-Bath Incubation in Wassermann Reaction.**—Ward Burdick, Denver, Col. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 163.

In the determination of syphilis by means of the Wassermann reaction prolonged, twelve hours, primary ice box incubation possesses decided advantages over the short period, one-half hour, incubator or water-bath treatment. Serums giving doubtful reactions by the latter method of primary incubation frequently are frankly positive by the former method. In the

series studied both methods gave uniformly negative results in 100 per cent of the clinically nonsyphilitic cases, and positive results in 100 per cent of the second stage untreated cases. In the second stage treated cases, however, there was a decided difference, especially in the higher percentage positives obtained by the prolonged primary ice box incubation method. Likewise this method gave a decidedly higher percentage of positives in the third stage untreated method) and the third stage treated cases. In the examination of spinal fluids (attaining 100 per cent as compared to 55 per cent by the half-hour water-bath from patients with cerebrospinal syphilis there frequently is obtained a positive reaction by the prolonged ice box incubation, whereas the conventional water-bath method may be negative.

**A Simple Method for the Removal of Natural Amboceptor from Human Sera.—**

R. L. Kahn, Lansing, Mich. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vi, p. 218.

For an amboceptor removal method to have wide acceptance, it must first be of proved efficacy; second, it must not render the sera anticomplementary and third, it must not be unduly time-consuming. The efficacy of this simple procedure is based on studies carried out in this laboratory on the rate of absorption of amboceptor by packed sheep-cells at various temperatures. A complete report of these studies will be presented in another paper. Suffice it to say in his connection, that it was observed that if an ordinary sized drop of packed sheep-cells is added to 1 c.c. of serum containing 200 units of amboceptor that this small quantity of blood will absorb as many as 160 units of amboceptor in 5 minutes at room temperature. The employment, therefore, of a ten minute absorption period in this procedure, gives a sufficient margin of safety for the absorption of far more amboceptor than is likely to be present in human serum. The author has further tested the dependability of his simple method in the following manner: After fixation of complement by serum and antigen in the regular Wassermann tests, sheep-cells were added (without amboceptor) and incubated in the water-bath at 37° C. for 10 minutes (Kaliski procedure). Natural amboceptor, if present, would thus have had ample time to produce hemolysis of the cells. He has not, however, observed a single instance of hemolysis—not even in the smallest degree—in 300 such tests carried out at different times, thus proving the efficacy of this procedure. It might be added that in his opinion, the slight dilution produced by a drop of packed cells in 1 c.c. of serum, does not affect the accuracy of the test. The cells are packed down by centrifugation for 14 minutes at 1600 r. p. m. and if the drop to begin with, is about  $\frac{1}{25}$  of a c.c. the amount of saline which remains with the serum, may safely be considered negligible. It is well known that sera acquire anticomplementary properties after prolonged extraction with red cells at incubator temperature, and in order to overcome this property, Rossi suggested a procedure for amboceptor absorption at low temperature. This worker employed chilled centrifuge tubes, chilled corpuscles, and centrifuged in the cold (during warm weather) after keeping the extraction mixture

in the ice chest for 30 minutes. The difficulty of applying this method on a comparatively large scale, is very evident. In his studies on the rate of absorption of amboceptor by sheep-cells, referred to above, the author has observed the occasional development of slight anticomplementary properties after a thirty minute, but not after a ten minute extraction period. This anticomplementary phase of our procedure is still under investigation, but there is every indication that a room temperature extraction lasting only 10 minutes, is not sufficient for the development of anticomplementary properties. Regarding the time-consuming element of his procedure, the author finds that it takes less than five minutes to add 100 drops of sheep-cells to the same number of serum tubes; 10 minutes to balance the tubes for centrifugation; 10 minutes for centrifugation, and 10 minutes to pour the supernatant clear sera in other tubes. These steps are carried out by one worker, while another is looking after the dilution and titration of complement. It is thus evident that the delay produced by this absorption procedure in the completion of the daily tests, is quite insignificant.

**Wassermann Reaction with Glycerolated Human Serum About Two Years Old.**

—E. H. Reudiger, Bismark, N. D. *Annals of Medicine*, 1920, vol. 1, p. 54.

Fifteen glycerolated human serums were kept in hermetically sealed glass ampules in a dark place at room temperature for about two years, after which time they were as suitable for the Wassermann reaction as they were when fresh. The results obtained with the syphilitic serums two years old were not quite identical with the results given by the same serums while fresh. In some instances the fresh serums gave stronger positive results than did the old serums; in other instances the old serums gave stronger results than did these same serums two years previously. Such or even greater differences than those recorded here may be due to technical variations, differences in complement or in antigen, or to differences in the proportions of various ingredients employed, and may be expected no matter how efficient may be the technic employed. The non-syphilitic serums gave uniformly negative results. In two years' time these serums had become but slightly anticomplementary and reheating the serums to 56° C. for thirty minutes removed the anticomplementary property without noticeably affecting the result given by the Wassermann reaction. All serums remained perfectly clear and sterile.

**A Positive Wassermann Test in Nonsyphilitic Patients after Intravenous Therapy.**—Albert Strickler, Henry G. Munson and David M. Sidlick, Philadelphia. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1488.

A positive complement-fixation test for syphilis obtained with the serum of a patient treated with arsphenamine for some nonsyphilitic malady or some obscure disease should be interpreted with great caution and considerable reservation. In view of the fact that there are a number of affections, such as



anemia, malaria, recurrent fever, pemphigus, psoriasis and septicemia, in which arsphenamine is recommended as a method of treatment, and because arsphenamine is employed at times in the treatment of obscure diseases and affections difficult to influence as a sort of last resort, it becomes the duty of the clinician and the serologist not to be over hasty or too dogmatic in pronouncing such an individual as definitely syphilitic. Only recently two such instances came under personal observation. One was a patient who presented a typical acne rosacea, and the other a patient who suffered from a Marjolin's ulcer of the left ankle. The latter patient received nine injections of arsphenamine and the former three injections before coming under the author's observation..

**The Value of Postmortem Wassermann Reactions.**—Stuart Graves, Louisville, Ky. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 592.

In ninety controlled cases there were flat discrepancies between antemortem and postmortem Wassermann reactions in only two. In 124 cases showing evidence of syphilis, postmortem or clinical, 137, or 90.5 per cent, gave a positive postmortem Wassermann reaction. The reliability of the Wassermann test depends to a considerable extent on the care used in obtaining and keeping the blood. Cholesterinized antigens are the most delicate and do not give false positive reactions if properly used and controlled. Observation of more than 15,000 reactions as correlated to clinical evidence substantiates the belief that the Wassermann test is the most delicate single test for syphilis. The postmortem Wassermann test is practically as reliable as the antemortem test if the serum is properly taken and shows nothing unusual in the serum control tube.

**The Provocative Procedures in the Diagnosis of Syphilis.**—Paul A. O'Leary, Rochester, Minn. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 348.

The provocative procedure employed by the Section of Dermatology and Syphilology of the Mayo Clinic consists of a single intravenous injection of 3 decigrams of arsphenamin, with a series of seven Wassermann tests made at twenty-four hour intervals, the first blood being drawn just before the arsphenamin injection, and if indicated, daily observation of the patient. Four factors contribute to the diagnostic worth of the procedure: (a) A true provocative effect on the Wassermann reaction. (b) The advantage of a series of Wassermann tests which strikes the average and assists in the interpretation of the spontaneous or technical variations of the ordinary Wassermann test. (c) An opportunity to observe a focal flare-up in a visible lesion, the "Jarisch-Herxheimer reaction." (d) The beginning of the therapeutic test. About one-fourth of the value of the procedure is ascribed to the provocative effect, one-half to the Wassermann series, and the remaining fourth is divided between the Herxheimer reaction and the therapeutic response elicited. The provocative procedure, including the Wassermann series, Herxheimer reaction, and

early therapeutic effect, adds about 16 per cent to the sensitiveness of a conservative Wassermann test in the diagnosis of syphilis. Although the author believes that gradations in the strength of the true provocative effect are not essential to a positive result, and although a single positive reaction among a number of negative reactions is usually significant, it must be remembered that the provocative procedure here described is subject to the same margin of error and calls for the same interpretation of serologic methods as the Wassermann reaction itself. False positive tests and persistent negative results in the presence of syphilis may occur, as in all Wassermann test technics. The use of hypersensitive antigens in a provocative procedure is to be deprecated, since they increase the risk of false positive results beyond the point justified by the general value of the procedure in diagnosis. A negative provocative test does not establish the fact of cure, but a positive provocative result is of assistance in recognizing an infection which might otherwise have remained concealed. The provocative procedure described is of no value alone, and should be regarded merely as a part of a general syphilogic examination. The procedure, for example, may yield negative results in the presence of positive spinal fluid findings. The provocative procedure is not a substitute for clinical judgment, and should be regarded in doubtful cases merely as the beginning of a therapeutic test.

**A Study of the Spinal Fluid in Fifty-two Cases of Congenital Syphilis.**—Lyle B. Kingery, Ann Arbor, Mich. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 12.

This study of selective cases emphasizes the important frequency with which cerebrospinal involvement is associated with prenatal syphilis. The importance of the routine lumbar puncture is again urged, not only because of its immediate value as a diagnostic procedure, but also on account of its influence on the ultimate prognosis in a given case.

**Interpretation of the "Paretic Curve" in Lange's Colloidal Gold Test.**—Lloyd James Thompson, Boston. *Archives of Neurology and Psychiatry*, 1921, vol. v, p. 131.

The paretic gold curve does not always indicate paresis, but, if used in conjunction with the other spinal fluid tests, it is a most valuable test for this disease. In some instances, this reaction is the deciding factor in the diagnosis of general paralysis. The vast majority of cases of paresis will give a paretic type of gold reaction. In a case that does not give such a reaction after more than one examination, the diagnosis of paresis is always questionable. The presence of paretic curves in almost 50 per cent of the cases of cerebrospinal syphilis shows that a paretic curve does not serve to differentiate paresis from this condition. However, the absence of a typical reading points strongly to cerebrospinal syphilis when the differential diagnosis lies between these two conditions. A paretic or marked syphilitic curve is to be expected in multiple

sclerosis. Besides paresis and multiple sclerosis, a paretic curve is occasionally found in the following conditions: tabes dorsalis, cerebrospinal syphilis, undifferentiated neurosyphilis, brain tumor, brain abscess, encephalitis, tuberculous meningitis, Korsakoff's psychosis (alcohol), eclampsia, epilepsy, lead poisoning (?) and drug addiction (?). The pathology of the above conditions would indicate more or less destruction of nerve cells in the brain, or, in other words, a parenchymatous involvement. It may be concluded, therefore, that a paretic curve points toward parenchymatous involvement of the brain, while the milder gold curves are obtained in meningitis, vascular disease and other conditions. The paretic curve is not only of diagnostic value, but also of prognostic value.

**Concerning the Colloidal Mastic Test.**—James M. Stanton, St. Louis. *Archives of Neurology and Psychiatry*, 1920, vol. iv, p. 301.

The results of the investigators who have made use of the mastic test (Emmanuel-Cutting) have been relatively discordant. The examination of fluids by both the colloidal gold and mastic tests has indicated that the information gained from the mastic test is in close agreement with that obtained from the gold test. Certain samples of gum mastic have been found to be entirely unsuited for use in performing the mastic test. This may serve to explain the conflicting reports of certain workers with this test.

**A Study of the Behavior of Syphilitic and Normal Sera Towards Certain Colloidal Solutions.**—V. R. Mason, Baltimore. *Bulletin of the Johns Hopkins Hospital*, 1920, vol. xxxi, p. 234.

Syphilitic sera can be shown to differ from normal in certain physical properties. This physical difference is possibly of fundamental importance in complement-fixation reactions, although at present its relation to immunity reactions is not clear. The Wassermann reaction and the flocculation reaction closely parallel each other.

**The Precipitin Test for Globulin in the Arachnoid Fluid in General Paralysis.**—Ludvig Hektoen and Clarence A. Neymann, Chicago. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1332.

On account of its simplicity, this test is well adapted to routine use. By using small tubes of a diameter of 5 mm. or so, only a small amount of anti-serum needs to be placed under each dilution of arachnoid fluid. It is essential, of course, that the fluid be drawn without admixture with blood.

**Provocative Reactions in the Cerebrospinal Fluid in Neurosyphilis.**—Harry C. Solomon, Boston, and Joseph Victor Klauder, Philadelphia. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 679.

Case histories are given to show that after treatment, the cerebrospinal fluid, which was negative before treatment, may become positive in all routine tests,



or a weakly reacting fluid may become much stronger. This is called a provocative reaction. It may be accomplished by the intravenous or intraspinal injection of arsphenamine. This is compared to the Herxheimer reaction or the production of neurorecurrences and is considered as the laboratory analogue. The provocative reactions are shown to occur in both the ventricular and spinal fluids. This is not a frequent phenomenon, and patients with vascular neurosyphilis with negative cerebrospinal fluids may not react in this manner. However, diagnosis may occasionally be made clear in obscure cases. In none of the cases in this series was the provocative obtained with the blood serum. Despite the increase in the strength of the spinal fluid reactions, clinical improvement may result, and continued treatment may again produce a negative fluid.

**Reinfection and Curability in Syphilis.**—Leo Jacobi, New York. *Archives of Dermatology and syphilology*, 1920, vol. ii, p. 493.

The question, "Is syphilis curable?" cannot be answered definitely in the light of our present knowledge. The occurrence of reinfection in syphilis may be accepted as an established fact. Reinfection, however, is by no means evidence of curability. These two conceptions do not stand and fall together, as many believe; they are not contingent on each other, and should be dissociated in the interest of clear thinking and unbiased judgment.

**Prophylaxis of Syphilis with Arsphenamine.**—Leo L. Michel and Herman Goodman, New York. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1768.

The authors have called attention to a method of preventing syphilis which they have found efficacious and which has not previously been described in the American literature. The injections of arsphenamine in small doses in persons who present no lesions, and who are definitely known to have been exposed to syphilitic infection, has in all the cases resulted successfully in acting as a prophylactic measure. The time since exposure has little bearing on the result, but must be taken into consideration when the minutiae of the procedure are under consideration. In two reported cases, a single injection has been held to be ample. In a patient under their own care, they intend to use a modification of the abortive cure, although she presents no lesions, because the date of first exposure is longer than the usual incubation time of syphilis. That the method will encounter objection has already been proved; but it will continue to be a procedure that will fill its place in the prophylaxis of syphilis.

**An Experimental Study of the Latent Syphilitic as a Carrier.**—Frederick Eberson and Martin F. Engman, St. Louis. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 160.

In this study, *Spirochete pallida* have been isolated in five instances from latent syphilitics—three times from inguinal glands (in two women and one

man) and twice from the semen. The strains produced typical syphilitic lesions in rabbits' testicles and could be recovered and propagated for an indefinite number of generations. The incubation periods of the spirochetes isolated from the glands were, respectively, fifty, fifty-four and 133 days, the last being doubtful owing to an early secondary infection in the experimental animal. The two strains that were isolated from the semen developed after four and seven months, respectively. *Spirochete pallida* was isolated from patients who gave a history of syphilis dating back eleven and thirteen years in two instances, and one year in three instances. An inguinal gland and the semen proved positive for spirochetes in the two cases first mentioned, and the glands and semen in the last named. In this series of positive results, a gland was found to be infectious in the case of a man whose Wassermann reaction had been negative, following treatment, and at the time of taking the specimen for the experiment gave a two-plus reaction only in the cholesterin antigen. A second instance of this nature was found in the case of a specimen of semen which proved positive for *Spirochete pallida*. As far as studies with these different strains have progressed, there is no indication that *Spirochete pallida* has lost its virulence for the rabbit. Detailed experiments on infectivity and other phases of experimental syphilis with these and other strains will be reported subsequently. It appears from this investigation, and that of others, that the blood and other body fluids, excepting semen, are not infectious in latent syphilis, or if so, but rarely. Incubation from blood in latent syphilitics did not favor any infectious property that might have existed. Thirty-six specimens, duplicates of those in the series, were incubated at 37° C. for from three days to four months before being injected into rabbits' testicles. The results were negative. One-third of the total number of spinal fluids from latent syphilitics evidenced lymphocytosis, and one gave a positive Wassermann reaction. Tonsils could not be studied, owing to severe secondary infections that were set up in the experimental animals. In one case, a dark-field examination showed what appeared to be *Spirochete pallida* in an emulsion of a tonsil taken from a child with a family history of syphilis, who gave a positive Wassermann reaction, although free from symptoms or visible lesions. The rabbits failed to survive injection of material. The groups of patients studied were composed of those that were untreated as well as those that had received no treatment within the last two years. Between the time of taking specimens for inoculations of rabbits and the first symptoms of a suggestive history of syphilis in these patients, from one to forty years had elapsed. Out of a total of 500 cases of syphilis which were seen at the clinic, seventy-five, or exactly 15 per cent, were definitely latent. These investigations demonstrate the fact that those persons that give a history of an old syphilitic infection may harbor active virulent *Spirochete pallida* for years, and this, in the face of irregular negative Wassermann reactions or slight reactions only in the cholesterin antigen.

**Further Progress in the Study of the Relative Efficiency of the Different Mercurial Preparations.**—Walter R. Ramsey and O. A. Groebner, St. Paul. *American Journal of Diseases of Children*, 1920, vol. xx, p. 199.

Mercurial ointment, 50 per cent, is to be preferred to the less concentrated forms and need not be repeated more often than twice weekly instead of daily. The quantity of mercury absorbed is much increased by friction. Calomel ointment is absorbed but less rapidly and to a less extent than the mercurial ointment and should, therefore, be given in greater concentration. The salicylate of mercury in oil should be given hypodermically twice weekly instead of once. The mercuric chloride, by hypodermic injections, although the dose is very small, continues to be eliminated for six or seven days. The fact, however, that its use frequently is followed by the appearance of protein in the urine should exclude it from the treatment of syphilis in children. Calomel by the mouth is absorbed in small amounts, and continues to be eliminated for a considerable time so that it is probable that it would be sufficient to give it at intervals of several days, thus avoiding diarrhea. Gray powder is absorbed to a small degree and eliminated rather rapidly so that large doses repeated daily would probably be necessary to maintain mercury in the circulation.

**Mercury Bichloride Intravenously.**—Carl H. Bastron, Lincoln, Nebraska. *American Journal of the Medical Sciences*, 1920, vol. clx, p. 118.

The one serious drawback to the intravenous injection of mercury is the frequent occurrence of thrombosis in the injected veins. The condition is not very painful but possesses the potential danger of causing embolism, and may preclude the continuation of the method itself by occluding all the available veins as well as bring the skill of the operator in question. The accident is somewhat less frequent if the mercury bichloride is suspended in serum before injection, but this modification is by no means thrombosis proof. Realizing this to be a serious drawback to the method the author hesitates to advocate its adoption by the profession as a routine practice. But in cases where quick results count for more than the local discomfort and slight chance of embolism would compel us to be cautious this method finds a proper place of application. Some day we may be in possession of a mercurial that is free from these objectionable features and equally as good or better than mercury bichloride in curative value. In that case the intravenous use of mercury will become as universal as that of arsphenamine is today.

**A Study of Mercury Injections by Means of the Roentgen Ray.**—H. N. Cole, Sidney Littmann and Torald Sollmann, Cleveland. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1559.

The absorption of "insoluble" mercury preparations from intramuscular injections can be followed admirably by roentgen-ray shadows. The method is not applicable to soluble preparations. An extensive study of clinical cases gave the following as the time when absorption is completed: Mercuric sali-



cylate: By gluteal muscles, mean, 4 days; extremes, 4 to 10 days. By lumbar muscles, mean  $8\frac{1}{2}$  days; extremes, 2 to beyond 24 days. Calomel: Mean, 15 days; extremes, 4 to 39 days. Gray oil: Unabsorbed during entire period of observation, a mean of 43 days; extremes of 16 to 125 days. These findings indicate that gray oil injections are both inefficient and dangerous, and their use should be abandoned. Calomel injections are also dangerous. Mercuric salicylate injections, especially into the gluteal muscles, give a satisfactory absorption and present relatively little danger.

**The Use of Arsphenamine in Nonsyphilitic Diseases.**—Matthew A. Reasoner and Henry J. Nichols, Washington, D. C. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 645.

For practical therapeutic purposes, the beneficial effects of arsphenamine and neoarsphenamine are most apparent in a limited number of spirochetal diseases. They act as a specific in Vincent's angina, relapsing fever, yaws, gangosa and pulmonary spirochetosis (if given early) in man, and in equine influenza. A therapeutic effect is noted in rat-bite disease in certain dental conditions and in fowl spirochetosis. The complete measure of the effect in the latter condition has not yet been established. No apparent benefit has been found in such other spirochetal diseases as Weil's disease and yellow fever. Good results have been obtained in syphilitics, in a number of nonsyphilitic conditions, which are influenced adversely by that disease. Their use has been recommended in conditions in which arsenic is indicated. In such case the effect is alterative rather than specific, and ordinarily there is no special advantage over liquor potassii arsenitis. There is a limited effect on certain protozoal diseases, as malaria (tertian and quotidian), some of the trypanosomiasis and leishmaniasis. It is possible, however, that this effect may be nonspecific. With the exception of anthrax, and possibly glanders, few favorable results are reported in bacterial diseases. Except in Vincent's angina, arsphenamine and neoarsphenamine should be administered intravenously in medium-sized dosage. Two or three injections usually accomplish the desired purpose, except in pulmonary spirochetosis, which may require a series of injections. In diseases showing liver involvement, it has been recommended that neoarsphenamine be given on account of its supposed lesser degree of toxicity.

**An Experimental Investigation of Certain Features of the Pharmacological Action of Salvarsan.**—D. E. Jackson and G. Raap, Cincinnati, Ohio. *Journal of Laboratory and Clinical Medicine*, 1920, vol. vi, p. 1.

First class preparations of salvarsan have almost no direct action on the bronchial musculature of the dog. It seems obvious that acute symptoms resembling anaphylactic shock, or the so-called "nitroid crises," if produced by good preparations of salvarsan cannot be due to a spasmodic contraction of the bronchioles. But we are not sure that this action might not occur in the case of especially toxic samples of the drug. The authors have studied the action of

salvarsan on the pulmonary pressure by means of an especially sensitive method. They believe that even the smallest injections of salvarsan exercise some immediate action on the pulmonary pressure. Its detection depends only on the sensitivity of the method employed for its investigation. When the pulmonary pressure has been greatly raised by salvarsan they have noted that injections of adrenalin tended to lower this pressure, and also to restore the excursions of the pulmonary pressure due to the respiratory movements of the lungs, when these had been previously greatly reduced by the salvarsan. They believe this results mainly from a mechanical shifting of the blood from the action of the adrenalin on the systemic vasculature. When solutions of salvarsan are injected into the general circulation by way of the femoral artery the pulmonary blood pressure is still raised by the drug. But the rise in pressure is less than if the drug were injected by the femoral vein. When solutions of salvarsan are injected into the portal vein and are thus carried through the liver before passing into the general circulation, then it is found that the drug produces but little if any effect on pulmonary pressure, although if the dosage is very large the pulmonary pressure may be raised slightly, apparently only as the result of an increased volume of fluid in the vessels. But toxic doses thus injected tend to lower the pulmonary pressure. They believe this action of the liver is brought about by a precipitation of the drug in the capillaries and arteries of the liver. This apparently does not correspond to the ordinary detoxicating action of the liver as manifested on many poisons. This precipitation in the liver takes place quickly and it does not prevent some of the drug from passing on into the general circulation, for the systemic pressure may fall to a proportionately much greater degree than does the pulmonary pressure.

**Reactions Following Intravenous Administration of Arsphenamine.**—Albert A. Strickler, Philadelphia. *New York Medical Journal*, 1920, vol. exii. p. 498.

As a result of his investigation, the author concludes that the injections of either atropine sulphate in the dose of one seventy-fifth of a grain or adrenalin chloride in the dose of 0.5 c.c. previous to arsphenamine injections, in no wise influences the occurrence of early reactive phenomena.

**The Effect of Shaking Alkalinized Aqueous Solutions of Arsphenamine and Aqueous Solutions of Neoarsphenamine in the Presence of Air.**—George B. Roth, U. S. P. H. S. *Public Health Reports*, 1920, vol. xxxv, p. 2205.

Shaking alkalinized aqueous solutions of arsphenamine or aqueous solutions of neoarsphenamine in the presence of air renders them highly toxic, as shown by intravenous administration to white rats. The increase in toxicity caused by such shaking is presumably due to the oxidation of these compounds to p-oxyphenylarsenoxide, commonly called "arsenoxide," inasmuch as shaking a solution of neoarsphenamine in the absence of air does not increase the toxicity of such a solution. The toxicity of alkalinized aqueous solutions of arsphen-

amine or aqueous solutions of neoarsphenamine is greatly influenced by the manner in which they are prepared for administration.

**The Chemistry of Arsphenamine and Its Relation to Toxicity.**—George W. Raiziss and A. Proskouriakoff, Philadelphia. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 280.

The quantitative determination of arsenic alone in arsphenamine is insufficient to estimate its purity. It is suggested to establish a ratio between the amounts of arsenic and nitrogen found by analysis. The degree of reduction in arsphenamine is best judged by estimating the ratio between the arsenic content and the amount of oxygen absorbed. The arsenic nitrogen and arsenic oxygen ratios indicate that various samples of arsphenamine are uniformly pure. Judged by the arsenic nitrogen and arsenic oxygen ratios, various preparations of arsphenamine rejected because of greater toxicity or severe reactions in patients appear to be as pure as those satisfactorily passing all tests. The analytical study of arsphenamine leads one to believe that the impurity causing reactions in patients is present only in very small quantities.

**Report on the Use of a Permanent Solution of Arsphenamine.**—Dudley D. Stetson, New York. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 324.

It is possible to prepare a solution of arsphenamine which will keep long enough to be of practical use. Observation thus far shows the solution tested (Arsphenamin-Lowy) to have a therapeutic value, apparently equal to that of the fresh solution.

**Summary of Experimental Studies on the Histopathologic Changes Produced By Arsphenamine and Neoarsphenamine.**—John A. Kolmer, and Baldwin Lucke, Philadelphia. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 289.

Neoarsphenamine behaves differently in the animal organism than arsphenamine and should not be regarded simply as arsphenamine in a convenient form for administration. When administered intravenously and at a constant rate, acid solutions of arsphenamine are much more toxic than the corresponding alkaline solutions, the toxicity of the acid solutions increasing with the concentration. A properly alkalized 2 per cent arsphenamine solution when administered intravenously and in high dosage is slightly more toxic than a 0.5 per cent solution. The toxicity of properly alkalized arsphenamine increases greatly as the rate of its intravenous administration is increased. Rate of administration is, therefore, an important factor in determining toxicity. When neoarsphenamine is found to dissolve with comparative difficulty, it is generally highly toxic and should be discarded. Shaking aqueous solutions of neoarsphenamine or alkalized arsphenamine in the presence of air increases their toxicity markedly. When a 4 per cent solution of neoarsphenamine is



shaken vigorously for ten minutes its toxicity is more than quadrupled. Arsphenamine preparations made in the United States are generally less toxic than those of foreign manufacture. Neoarsphenamine preparations made in the United States compare favorably, and in certain instances are decidedly less toxic than most of the foreign products.

**A Clinical Study of the Reactions Following the Intravenous Administration of Arsphenamine in Nonsyphilitic Persons.**—Albert Strickler, H. G. Munson, D. M. Sidlick and A. Strauss, Philadelphia. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 692.

Both syphilitic and nonsyphilitic patients may experience similar reactions following the intravenous injections of arsphenamine. The endotoxins, produced presumably by the rapid killing of spirochetes in the blood stream of syphilitic patients, play either no rôle or a very unimportant one in the causation of reactive symptoms. The percentage of reactive symptoms following intravenous injections of arsphenamine is equal in both syphilitic and nonsyphilitic patients. It is our impression that the two most important factors in the production of arsphenamine reactions are (1) the patient and (2) the medicament. Of these two factors, the medicament is far more potent in causing reactive symptoms; the untoward phenomena may be produced either by some impurity in the arsphenamine or by some chemical reaction between the arsphenamine and the chemical constituents of the blood, or both factors may be operative at the same time.

**A Comparative Study of the Trypanocidal Activity of Arsphenamine and Neoarsphenamine.**—Jay F. Schamberg, John A. Kolmer and George W. Raiziss, Philadelphia. *American Journal of the Medical Sciences*, 1920, vol. clx, p. 25.

Trypanocidal tests employing rats infected with *T. equiperdum* provide a means for determining the curative properties of arsphenamine and neoarsphenamine. Such medicinals as arsphenamine and neoarsphenamine proving trypanocidal in vivo are probably curative in syphilis; other compounds as the mercurials, which are unable to influence experimental trypanosomiasis, may still influence infections with *T. pallida*; trypanocidal tests possess, therefore, a greater positive than negative value in chemotherapeutic studies in syphilis. In conducting trypanocidal tests the virulence of the strain, the method of infection, the interval between infection and treatment and the weight of the test animals are modifying factors and must be rendered uniform to secure satisfactory results. With the strain of *T. equiperdum* employed in these experiments the smallest amounts of arsphenamine sterilizing rats infected twenty-four hours previously varied from 0.010 to 0.030 gm. per kilo of body weight, the general average for twenty-one compounds prepared by six different laboratories, being 0.023 gm. per kilo of rat. The smallest sterilizing doses of neoarsphenamine under identical conditions varied from 0.020 gm. to

more than 0.040 gm. per kilo of rat; the general average for twenty-two compounds from six different laboratories was about 0.040 gm. per kilo. The trypanocidal activity of different lots of arsphenamine and neoarsphenamine prepared by the same laboratory and by different laboratories varied in a manner analogous to variations in lethal toxicity for rats. The trypanocidal activity of arsphenamine is 1.74 times greater than that of neoarsphenamine; in experimental infections with *S. obermeieri*, hen spirillosis and rabbit syphilis, Castelli found arsphenamine from 1.5 to 1.78 times more active therapeutically than neoarsphenamine. According to these results 0.6 gm. arsphenamine equals 1.05 rather than 0.9 gm. of neoarsphenamine in therapeutic activity. The trypanocidal dose (*dosis therapeutica*) of arsphenamine is 4.56 times less the highest tolerated dose for the rat (*dosis tolerata*); the trypanocidal dose of neoarsphenamine is 6.35 times less the highest tolerated dose. These results indicate that neoarsphenamine is a somewhat safer compound than arsphenamine; even when 1 gm. of neoarsphenamine is administered as equivalent in therapeutic activity to 0.6 gm. arsphenamine, the margin of safety is greater.

**Comparative Studies of the Toxicity of Arsphenamine and Neoarsphenamine.**

—Jay F. Schamberg, John A. Kolmer and George W. Raiziss, Philadelphia. American Journal of the Medical Sciences, 1920, vol. clx, p. 188.

Toxicity tests of arsphenamine and neoarsphenamine among the lower animals possess definite practical value as a means of establishing standards of purity for these compounds. These toxicity tests are best conducted by injecting solutions of the drugs intravenously inasmuch as this is the usual method of administration in the treatment of syphilis and the results are sharper than observed with subcutaneous injections. Animal tests show "lethal toxicity" only, that is, the duration of life after the administration of given amounts per gram of body weight; they do not give rise to the transient untoward effects of arsphenamine and neoarsphenamine ascribed to faults of technic in the preparation and injection of the solutions and the presence of an unidentified toxic substance designated as "X," which we believe may be present in the compounds themselves and produce the "nitroid crisis." The highest tolerated doses of arsphenamine and neoarsphenamine administered by intravenous injection to healthy rats are about 0.105 and 0.254 gm. per kilogram of body weight respectively; neoarsphenamine is therefore about 2.4 times less toxic than arsphenamine. Calculated upon the basis of seventy kilograms as the body weight of an average person, the highest tolerated dose of arsphenamine may be placed at 7.35 gm. and of neoarsphenamine at 17.5 gm., providing the tissues of persons are approximately of the same susceptibility; comparative tests among rabbits, rats and mice in which the same amounts of drugs were given per gram of body weight indicate, however, that the larger and heavier animals are more susceptible and very probably human subjects cannot tolerate these substances in doses proportionate to body weight as established in animals. By subcutaneous injection in mice neoarsphenamine was found to be half as toxic as arsphenamine but when administered subcu-



taneously to rats, neoarsphenamine was found twice as toxic as arsphenamine. Insofar as the toxicity of arsphenamine and neoarsphenamine, may be determined by intravenous injection of solutions in rats, the single dose of arsphenamine commonly administered (0.6 gm.) may be said to be about twelve times less than the highest tolerated dose and the highest single dose of neoarsphenamine commonly injected (0.9 gm.) is about nineteen times less; from the standpoint of margin of safety larger amounts of neoarsphenamine may be given and maintain the same ratio between *dosis therapeutica* and *dosis tolerata*, as apparently exists with arsphenamine.

**Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis.—**

John H. Stokes, Rudolph Ruedemann, Jr., and Willis S. Lemon, Rochester, Minn. *Archives of Internal Medicine*, 1920, vol. xxvi, p. 521.

Jaundice as a complication of the treatment of syphilis in the Section on Dermatology and Syphilology of the Mayo Clinic was a relatively rare occurrence during the period from August, 1916, to August, 1918. From August, 1918, to July, 1920, the incidence of this complication has increased over 1,000 per cent. During the period from January, 1917, to July, 1920, there have been no notable changes in the technic of routine treatment of syphilis in this section, and one of the most reliable brands of arsphenamine and neoarsphenamine has been consistently employed throughout the entire period, with a steady diminution of other types of complications. Neither have there been any conspicuous changes in the types of syphilis treated. It is scarcely reasonable, therefore, to conclude *a priori*, that because most of the patients had syphilis and were treated for it, either syphilis or antisyphilitic treatment was responsible for the enormous increase in the incidence of jaundice among them. This increase amounted to four times the maximum expectancy of jaundice as a complication according to the Meirowsky statistics based on 225,780 injections. A critical examination of the data obtained from the seventy cases occurring among their patients indicates that while several distinct types of jaundice are probably represented in the series, the large proportion were not ascribable directly if at all to the effects of syphilis, or of antisyphilitic treatment with either arsphenamine or mercury. Syphilis as either a primary or a secondary etiology is largely excluded by the fact that the overwhelming proportion of the patients had had so much treatment before jaundice that Herxheimer effects and hepatorecurrences were practically eliminated. Moreover, two-thirds of the patients recovered while antisyphilitic treatment was suspended, and one-fourth of those who recovered were in fact not again treated for the disease after the jaundice appeared. Four of the patients who were jaundiced did not have syphilis. The argument against an arsphenamine etiology is based on the fact that no definite time sequence between the administration of arsphenamine and the incidence of jaundice can be detected, jaundice often appearing so late that any connection between the two occurrences is merely a matter for speculation. There was no constant relationship between the total dosage of arsphenamine administered and the severity of the



hepatic symptoms which could not be largely explained on the basis of the time intervals in the interim home treatment system of the department. Arsphenamine had almost no unfavorable effect on those patients who continued it during their jaundice (16 per cent of the series), and resumption of the arsphenamine in 50 per cent of their patients as soon as their jaundice cleared up had no effect in producing relapse. Jaundice occurred in patients receiving neoarsphenamine in isotonic solution, as well as in those receiving arsphenamine, so that a hemolytic influence of the drug seems not to be a factor. Similar arguments applied in demonstrating the probable lack of relation between the administration of mercury and the incidence of jaundice lead to similar conclusions. Six of the jaundiced patients had never received mercury and several others had had insignificant amounts. Three received it throughout their jaundice without ill effect. The study of this series of seventy cases discloses strong circumstantial evidence to the effect that an infectious agent, possibly associated with epidemic respiratory infections, is the exciting cause of the wave of jaundice observed since August, 1919. The overwhelming proportion of the incidence of jaundice occurred between October, 1919, and April, 1920, with peaks in November and February. Prior to November, 1919, 80 per cent of the seventy patients had received arsphenamine, but only 31.5 per cent had developed jaundice. The remaining 52 per cent not thus far jaundiced were, therefore, precipitated into the complication between November and April by some extraneous factor. The months of maximum incidence of jaundice were those of epidemic respiratory and systemic infection, including influenza. Forty-one per cent of the patients of this series had coryza, tonsillitis, pharyngitis, influenza, "grippe," bronchitis, pneumonia or otitis media (named in order of frequency), intimately associated with the prodromal symptoms or actual appearance of the jaundice. Symptoms suggestive of a systemic infection, with lassitude, arthritis and myalgia, backache, anorexia, nausea and vomiting, diarrhea or constipation, headache, dizziness, loss of weight, and nonlocalizable abdominal distress, usually preceded by several days or weeks, the onset of the jaundice and of hepatic symptoms as such. The administration of ox-gall in tablet form seemed of some benefit in shortening the course of the jaundice in twenty-four of these cases. Fifty-nine per cent of the cases were associated with epidemics of colds and influenza in the vicinity. One-fourth of the patients gave histories of jaundice developing in their localities, often in relatives, neighbors, and friends. Four of six physicians testified to an association of jaundice with coryza, pharyngitis, and influenza in their recent experience. Two testified to epidemic features during the months included in the survey. A total of 73 per cent of their cases yielded one or another contributory evidence of a possible infectious factor in the etiology of the jaundice. Incomplete bacteriologic studies of seven cases were unsuccessful in identifying a causative organism. Study of the recent literature after their impressions were formed supplied confirmatory evidence that a form of nonspirochetal catarrhal jaundice of unknown etiology is coming into medical recognition, and has at various times and places in this country, Europe, and

Asia, attained to epidemic proportions. This type of jaundice exhibits many of the salient features presented by the large proportion of these cases. The possibility that this type of jaundice may be masquerading as syphilis or as an arsenical complication of antisypilitic treatment has been overlooked by recent writers on the subject, and undue aspersion, perhaps, has been cast on modern syphilotherapeutic methods. This is especially true since no arsenic could be found in the urines or in the livers in necropsied cases. This apparently epidemic jaundice is associated with a hepatitis often closely simulating that produced by the heavy metals. Laboratory studies and the literature suggest that the jaundice is, in part, hematogenous and associated with gastrointestinal lesions. The intensity of the hematogenous phase is proportional to the illness of the patient and is mild or absent in mild attacks. The relation between influenza and the type of jaundice discussed is problematical. Little or no jaundice appeared among their patients during the influenza epidemic of 1918, and the time of incidence of the complication in 1919 and 1920 has been approximately but not exactly that of influenza. About 400 cases of influenza observed in the Clinic by one of the authors showed no special tendency to develop jaundice as a complication. It must be recalled, however, that the seventy cases here considered were collected from among a total of 5,200 patients. It is possible that the condition is a sequel or modification of epidemic influenza, rather than a direct complication. The authors do not regard their contentions as proved conclusively. They believe, however, that while any agent potentially injurious to the parenchyma of the liver, such as arsphenamine, may, and probably does, act as a predisposing cause in the cases of hepatitis that have recently become so comparatively numerous in their experience, the exciting cause is probably an as yet unidentified infectious agent. This agent may be responsible for varying grades of hepatitis, ranging from mild cholangitis to extensive destruction of the affected organ, suggesting acute yellow atrophy.

**A Clinical Study of Wassermann-fast Syphilis, with Special Reference to Prognosis and Treatment.**—John H. Stokes and George J. Busman, Rochester, Minn. *American Journal of the Medical Sciences*, 1920, vol. clx, p. 658.

Of 458 syphilitic patients who had received from twelve to twenty-nine arsphenamine injections combined with mercurial inunctions, the average being fourteen injections and ninety inunctions in eleven months, 6.6 per cent of primary and secondary cases and 101, 22 per cent, of latent, late and hereditary cases (average duration thirteen years) remained persistently Wassermann positive. Cardiovascular changes are apparently those most likely to underlie a resistant positive Wassermann test in late syphilis (44 per cent), with neurosyphilis 30 per cent, osseous lesions 30 per cent, hepatic, splenic, and gastric syphilis 21 per cent, and other types from 10 to 17 per cent. More than one type of involvement was the rule in the individual cases of this group. There were only 10 patients presenting no other evidence of syphilis than their positive Wassermans. Patients with syphilis should therefore be studied



from other angles than that of the presenting type of involvement, in the effort properly to appraise their condition and susceptibility to treatment. Sixty-five per cent of the patients with cardiovascular syphilis had aortitis and 60 per cent myocardial changes. Of the neurosyphilitics, 40 per cent had paresis and 50 per cent clinical tabes dorsalis. Fifty per cent of patients with neurosyphilis had cardiovascular syphilis also. Gastric and hepatic syphilis were recognized in 52 and 47 per cent of the visceral cases as against only 14 per cent presenting recognizable splenic involvement. Patients with cutaneous syphilis showed the familiar immunity from neurosyphilis and the reverse. While pyogenic foci were present in 74 per cent of the patients with resistant Wassermann reactions no frank etiologic connection was apparent. The same was true of alcohol, which was used by only 12 per cent of these patients. There was no evidence that Wassermann-fastness is the result of infection with any special strain of organism. In fact, the "polystructural" involvement in such cases suggests the contrary. Eighty-four per cent of the patients in the authors' resistant group have undergone symptomatic arrest today under the treatment received. Paresis and tabes dorsalis with gastric crises formed more than half the failures. The amount of treatment to which a Wassermann-resistant patient should be subjected cannot be exactly defined. The principles employed in making a decision, which are in effect the principles underlying the therapy of all late syphilis are discussed in the paper. In particular, reversal of the Wassermann, while desirable, should not be the primary aim of the therapy. Symptomatic response, with arrest of the process, and the giving of as much treatment as to an early case, provided tolerance permits, are the important considerations. A persistently positive serum Wassermann reaction seems to be an accompaniment of grave rather than of trivial syphilis. At least such is the case in enough instances to suggest the need for the most painstaking and repeated investigation of the clinical aspects of the Wassermann-fast case. Premature statements based on insufficient evidence as to the insignificance of a fixed positive Wassermann reaction are to be deprecated. Wassermann-fast patients should not be discharged from periodic careful reexamination, with special reference to the cardiovascular and nervous systems throughout life. The frequency of such examinations should be dictated by the gravity and extent of the original process and the degree of apparent resistance to treatment.

**Treatment of Disorders of the Spinal System by the Intraspinal Method and Its Value to the Business Man.**—Frederic J. Farnell, Providence, R. I. *Journal of Nervous and Mental Diseases*, 1920, vol. li, p. 420.

Since the two usual obstacles in the way of the business man who seeks treatment for disease of the spinal nervous system are fear of "puncture headache" and the insistent protection used by the average physician, that of keeping the patient in bed, there is little doubt but that many patients delay indefinitely their treatment and may even reach a stage where actual destruction has taken place with not only a permanent physical disability but many times a partial if not a permanent economic difficulty. It, therefore, occurred



frequently in the mind of the writer that it might be possible to utilize the apparently large extra-dural space which contains great amounts of areolar tissue well vascularized and containing many lymphatics. With that in view and also the possibility of inactivated serum passing by the process of dialysis into the spinal fluid system a series of cases were treated by what might be called the modified (Farnell) intraspinal method,—namely, injection of salvarsanized serum into the extra-dural space whereby a serum can be introduced without the removal of spinal fluid thus avoiding, as very often occurs in early cases, a “puncture headache” and also the unnecessary problem of “going to bed” and at the same time keeping the man at his vocation which is a very important factor in this epoch. It should be stated that all these patients received a lumbar puncture in order to clearly diagnosticate their condition and with the exception of five all suffered from what has been termed a “puncture headache.” The majority of the ten who had “puncture headaches” spent the greater part of one week in bed, much to their dislike and to the disappointment of their employers. This reinforced, naturally, the feeling of the writer to attempt to treat these patients with salvarsanized serum introduced into the extra-dural space. By this method approximately seventy per cent improved rapidly so that after from ten to fifteen extra-dural injections they were considered not only free from the symptoms from which they primarily complained but also showed a change in their neurophysical complex. Three cases that are considered well enough to cease treatment show a negative blood for the Wassermann reaction and a negative spinal fluid for the Wassermann reaction also (these patients again were laid up with a “puncture headache”). It does seem, therefore, that the extra-dural treatment as here described should be considered as a part of the therapeutic procedure in such cases as do not respond to the intravenous method of treatment. It is also suggested that it might be used as a reinforcement to the intravenous method of treatment because of the fact that it does not interfere with the patient’s usefulness to himself and society through his vocation.

**Intracistern Injections of Salvarsanized Serum in Neurosyphilis.**—Henry McCusker, Providence, R. I. *Boston Medical and Surgical Journal*, 1920, vol. clxxxiii, p. 490.

Cistern puncture offers another route of application in the method of therapy in syphilis of the central nervous system. It gets the serum nearer to the seat of the disease. It is easier to accomplish than a spinal tap. It offers no more danger than rhachicentesis.

**Intraspinal Treatment in Neurosyphilis.**—James Herbert Mitchell, Chicago. *Archives of Dermatology and Syphilology*, 1920, vol. 2, p. 44.

The Swift-Ellis intraspinal method of treatment of syphilis of the central nervous system is superior to intensive intravenous treatment alone. Whether the efficacy of the method of treatment depends on (a) the irritative action of

the serum, thereby increasing the permeability of the chorioid plexus for arsphenamine; on (b) the spirocheticidal action of the arsphenaminized serum, or on (c) spinal drainage, remains to be determined. The method is perfectly safe when care is exercised in technic and in the proper selection of cases, and should be resorted to in all cases in which the patient fails to respond to intravenous medication.

**A Method of Treating Congenital Syphilis.**—John A. Fordyce and Isadore Rosen, New York. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1385.

The earlier treatment is begun, the better are the chances of cure. Systematic treatment with soluble mercury in oil and neoarsphenamine given intramuscularly is so simple and the results are so gratifying that serologic cures may be anticipated within one year of interrupted treatment. The Wassermann test taken at birth in the infant is not to be relied on. Ten days after birth is a better time for accurate interpretation of the serology. A negative Wassermann test in the face of positive clinical manifestations may occur in congenital syphilis; therefore, careful clinical examination is very important, and antisymphilitic treatment may be instituted with negative serology.

## BOOK NOTICES

(Books for review should be sent to Dr. W. H. Deaderick, Associate Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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**A TEXT BOOK OF DERMATOLOGY.**—By J. Darrier, Physician to the Hospital Saint-Louis, Member of the Academy of Medicine, Paris, France; Honorary Member of the American Dermatological Association, etc. Authorized Translation from the Second French Edition. Edited with notes by S. Pollitzer, New York. 769 pages, illustrated with 204 engravings and 4 colored plates. Philadelphia and New York, Lea and Febiger, 1920. Price \$8.50.

This work is divided into two parts, Part I, Morphology of the Dermatoses and Part II, Nosology of the Dermatoses, while in an ample appendix therapeutic notes are considered. At the end of each section is indicated briefly the kind of medication adapted to the disease under consideration and in the appendix greater detail concerning some of the modes of treatment is entered into. The book having been written for students and general practitioners has been made as concise and practical as possible, bibliography, historical references, quotations and academic discussions having been omitted. The material has been arranged according to the author's own plan which an introduction seems amply to justify. Syphilis receives full consideration. Mercury is advocated by injections on the grounds that they insure strict dosage, exclude fraud or negligence on the part of the patient and spare the digestive apparatus. The author prefers a soluble preparation and the benzoate, bibromide, biniodide or the cyanide are given the preference. He states that arsenobenzol is the most active and the most permanently sterilizing antisyphilitic remedy known. The editorial notes enhance the value of the work which is a valuable addition to the library, not only of students and general practitioners, but of dermatologists as well.



# Index to Current Syphilis Literature

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## A

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## Original Articles

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### VENEREAL DISEASE CONTROL

BY C. C. PIERCE, ASSISTANT SURGEON GENERAL

U. S. PUBLIC HEALTH SERVICE

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THE prevalence of venereal diseases is now a matter of concern to thinking people throughout the civilized world. There has been within the last few years a widespread movement in Europe as well as in America to promote facilities for the treatment and prevention of these diseases, which constitute a now clearly recognized twofold danger to civilization—syphilis as a cause of degeneracy and insanity; gonorrhea as a cause of blindness and both syphilis and gonorrhea as potent causes of social damage, ill-health and sterility.

The Division of Venereal Diseases of the U. S. Public Health Service was created through the passage by Congress July, 1918, of the Chamberlain-Kahn Bill, which appropriated more than two million dollars for venereal disease control by state boards of health and the Public Health Service. Before this time there had been no federal effort to combat venereal diseases in the United States. It can be seen from this fact that the present national movement against venereal diseases is of very recent origin, dating back less than three years. By this bill

the duties given to the Division of Venereal Diseases included: (1) The study and investigation of the cause, treatment and prevention of venereal diseases. (2) Cooperation with the State departments of health for the prevention and control of such diseases within the state. (3) The control and prevention of the spread of these diseases through interstate traffic.

The immediate cause of the passage of this legislation was the discovery that of the second million drafted men examined upon their arrival at camp, 5.4 per cent, or about 6 out of every hundred had a venereal disease, in a sufficiently active form to be diagnosed on inspection. This percentage included only obvious cases of gonorrhea, syphilis and chaneroid. Wassermann examinations were not made, neither were any tests for the gonococcus carried out; the actual number of cases of venereal infection must therefore have been many times that actually reported. Such figures as these brought the realization that drastic action was necessary, since they implied a higher percentage of venereal disease among the civil population than had hitherto been thought to exist.

The activities of the Division of Venereal Diseases may be classified under two heads: medical and preventive. The medical activities properly carried out are also of great value in preventing other infections and will be largely considered in this paper, although the other preventive measures are regarded as of great importance. The medical measures have as their aim efficient treatment for all persons infected. Efforts have been made to secure the interest and cooperation of physicians in reporting venereal diseases and the special training of physicians and nurses in the treatment and prevention of venereal diseases, the cooperation of dentists, and the establishment and efficient functioning of clinics where those unable to pay may secure free treatment. The preventive measures comprise both legislative and educational activities.

## I. MEDICAL MEASURES

### REPORTING

The aim of the campaign with physicians is not only that they may understand the proper methods of treatment, but also that they may realize the necessity of reporting cases of venereal disease to the state boards of health and report such cases promptly and conscientiously.

There is hardly a paper written on the subject of venereal disease



which does not stress the importance of securing accurate figures as to the extent of syphilis, gonorrhea and chancroid among the general population. And yet it may be stated that at present there are no accurate statistics available as to the mortality or morbidity caused by these diseases among the general population of any country. Various estimates have, of course, been made and numerous investigations have been carried out among selected classes of people.

Because of this lack of information it was plain that the first step to facilitate medical measures must be the reporting of these contagious diseases, so that a knowledge of their extent and distribution might be gained. One of the conditions therefore, that must be complied with by a state before participating in the Chamberlain-Kahn fund, is the existence of a reporting law. Since July 1918, monthly reports have been received from all states participating in the fund and these figures are available.

It is hardly necessary to point out that the figures cannot be supposed to show the incidence of venereal disease, first because many infected persons do not consult a physician for treatment, and secondly, because not all physicians have yet been brought to a realization of the importance of reporting all of their cases. What the figures do show, however, is that progress is being made in this direction and that in time figures reported in this manner may be taken as a real index of venereal infection in the country.

A comparison of the figures available for 1919 and 1920 may be of interest. In 1919 there were reported to the state boards of health 131,193 cases of gonorrhea; 100,466 cases of syphilis; 7,843 cases of chancroid and others; or a total of 239,502 cases of venereal disease. In 1920 there were reported to the state boards of health 172,387 cases of gonorrhea, 142,869 cases of syphilis; 10,861 cases of chancroid and others; or a total of 326,117 cases of venereal disease. The total increase of cases reported during the past year, therefore, has been 86,615 cases or 36 per cent. This of course does not mean that there were any more cases of venereal disease in the United States in 1920 than there were in 1919, but merely that there was greater efficiency in reporting.

#### WORK WITH PHYSICIANS, DENTISTS, AND NURSES

Various methods have been used to awaken the interest of the medical profession in venereal disease control. In the first year of the

work a campaign was carried on among physicians so that they might be impressed with the seriousness of the problem of venereal disease control and realize their responsibility to the public in carrying out the program, through the prompt reporting of diseases coming to their attention and also to give to each physician an opportunity to secure a copy of the standard "Manual of Treatment of the Venereal Diseases" as revised by the Service.

As a result of this appeal agreement cards and favorable replies were received from 60,666 physicians, or nearly 50 per cent of the medical profession in the United States. The various states have purchased numerous copies of the manual and distributed them, and where this could not be carried out through the agency of the states the Service has furnished copies of the manual.

Dentists have also been circularized and their cooperation secured. A course for graduate nurses in medical social service, so important in the rapid extension of clinic facilities, was arranged by the Public Health Service in cooperation with the Red Cross, Columbia University, Bellevue Hospital, and the New York School of Social Work. This course began in July, 1919, lasted four months, and was most successful. It is interesting to note that each of the nurses enrolled secured a position in public health work at the close of the course.

#### WORK WITH RAILROAD SURGEONS

It should be mentioned here, in connection with securing the cooperation of physicians, that some interesting work has been done with various railroad surgeons, as part of the Industrial Program of the Division. Two conferences were held, one for roads east of the Mississippi and one for roads west of the Mississippi. It may be of value to deal with this phase of the work somewhat fully in order to show in this particular instance just what were the results accomplished by interesting a single group of physicians.

At these conferences data very valuable from a public health point of view were presented by the surgeons of the several roads. Heretofore no definite or concerted effort had been made to do any preventive work, so far as venereal diseases were concerned, although railroad surgeons realized in a general way that syphilis, particularly, figures in the number of accidents. However, each case in the past was dealt with as it developed and usually after some untoward happening or some accident which was both fatal and costly. Chief surgeons who

came to the conference doubtful of the good that could be accomplished entered into a general plan with those who were more optimistic at the start with the result that by July, 1920, twenty-two railroads had arranged to buy educational material and a number of others had arranged to use that available from the states free.

Lecture tours were arranged by some railroads. Other railroads adjusted their medical service to include diagnosis and treatment for venereal diseases and the railroads large and small undertook to establish a relationship of confidence between the medical department and the employes who might be infected with either gonorrhea or syphilis.

It is interesting here to note that the chief surgeon of one large railroad at the conference at Atlantic City reported that investigations had shown four comparatively recent wrecks to be due to a mental lapse on the part of engineers who were found to be in the early stages of paresis.

Another chief surgeon reported that one of his engineers after leaving his run one night had done bodily harm to his wife and daughter, and three hours afterwards was entirely oblivious to his actions. This case on final investigation proved to be paresis in the early stages, and his condition one entirely unfitting him for responsibility of running an engine.

About this time Dr. John H. Stokes, of the Mayo Clinic, had made an interesting study which showed that syphilis was about eight times as frequent among railroad men and their families as any other occupational group which came to the Mayo Clinic at Rochester, Minnesota. These disclosures and others made at the several conferences resulted in extra efforts being made to bring about some understanding between the men and company officials as to the need of eliminating syphilitics from responsible positions in railroad work, where men are entrusted with the life of passengers and other workmen. Also, these conferences and the venereal disease control work have stimulated railroad surgeons to increase preventive activities and have caused them to look more sharply for syphilis both in preliminary physical examinations and in investigating wrecks.

#### CASE HISTORIES AND ABSTRACTS

Included in the list of these various medical activities which are also educational, mention should be made of the case histories of



syphilis and gonorrhea, and of the abstracts from current medical literature which are supplied to physicians. Case reports from the Massachusetts General Hospital giving detailed accounts of cases of syphilis difficult of diagnosis and the methods used to secure adequate diagnosis, treatment given, and the results obtained, have been disseminated among the physicians of the various states by many state boards of health. Abstracts of current medical literature dealing with venereal diseases are compiled by the Division of Venereal Diseases every month and are supplied to State health officers, venereal disease control officers and to medical journals and physicians who request copies.

#### THE INSTITUTE ON VENEREAL DISEASE CONTROL AND SOCIAL HYGIENE

Aside from these general measures, it is probable that the most important agency employed for the purpose of arousing the interest of physicians and nurses in venereal disease control and in giving instruction in methods of treatment, social service and allied subjects, has been the Institute on Venereal Disease Control and Social Hygiene, conducted by the Public Health Service, November 22 to December 4, 1920, at the New National Museum, Smithsonian Institute, Washington, D. C.

Although this institute was designed to make available to those employed in any capacity in the attack upon venereal diseases the most recent contributions to knowledge and experience along these lines, it reached more physicians than workers of any other class. More than one-third of the total registration of over 600 was composed of members of the medical profession. The medical courses were extremely complete and were conducted by some of the most prominent authorities in this country. They included lectures by Doctors John A. Fordyce, John H. Stokes, H. H. Hazen, Edward L. Keyes, Charles C. Norris, Hugh H. Young, J. T. Geraghty, H. A. Fowler, and demonstrations by Doctors G. C. Lake, H. G. Irvine, W. H. Hough, H. J. Nichols, H. A. Fowler and Charles C. Norris. The medical section of the program was as follows:

##### 1. *The Diagnosis and Treatment of Syphilis*

1. General pathology .....Dr. Fordyce
2. Primary lesions .....Dr. Fordyce
3. Skin manifestations .....Dr. Fordyce
4. Visceral lesions .....Dr. Fordyce
5. The problem of syphilis in general diagnosis.....Dr. Stokes

6. Familial, antenatal, and congenital syphilis.....Dr. Stokes
7. The arsphenamine phase of treatment.....Dr. Stokes
8. The mercurial phase of treatment.....Dr. Stokes
9. The general management of the syphilitic.....Dr. Stokes
10. Review

2. *The Diagnosis and Treatment of Gonorrhea*

1. Clinical pathology of gonorrhea in the male.....Dr. Keyes
2. The cure of gonorrhea in the male.....Dr. Keyes
3. The communicability of gonorrhea in the male.....Dr. Keyes
4. Gonorrhea in the female.....Dr. Norris
5. Gonorrhea in the female.....Dr. Norris
6. The treatment of gonorrhea in the A. E. F.....Dr. Young
7. Chronic inflammation of the prostate and seminal vesicles....Dr. Young
8. Importance of a correct diagnosis for the treatment of  
urethritis .....Dr. Geraghty
9. The complications of gonorrhea and their treatment.....Dr. Fowler
10. Review

3. *Advanced Course in the Treatment of Syphilis and Gonorrhea*

1. Clinical pathology of gonorrhea in the male.....Dr. Keyes
2. Cure and communicability of gonorrhea in the male.....Dr. Keyes
3. Neurosyphilis .....Dr. Fordyce
4. Neurosyphilis .....Dr. Fordyce
5. A clinical interpretation of diagnostic tests.....Dr. Stokes
6. The general management of the syphilitic.....Dr. Stokes

*Demonstrations, Amphitheater, Freedman's Hospital*

A well arranged amphitheater with modern equipment was made available at the Freedman's Hospital. Clinical material was provided in advance for these demonstrations.

Wednesday, December 1, 3 P.M. Syphilis

- (a) Arsphenamine administration.....Dr. Lake
- (b) Administration of mercury.....Dr. Irvine

Thursday, December 2, 2 P.M. Syphilis

- (a) Diagnosis and treatment of cerebrospinal syphilis.....Dr. Hough
- (b) Demonstration of treponema.....Dr. Nichols

Friday, December 3, 2 P.M. Gonorrhea

- Epididymitis and prostatitis .....Dr. Fowler

Saturday, December 4, 2 P.M. Gonorrhea

- (continued) .....Dr. Norris

As registrants for the Institute came from forty-three states, the District of Columbia, Philippine Islands, Canada, Chili, Mexico, Peru, and Switzerland, it is evident that the physicians registering came from widely scattered communities and that their influence would be widely disseminated.

So successful was the Institute in Washington that since that time through the activities of various Health Departments smaller State Institutes, aiming to instruct physicians in the technic of venereal disease treatment have been held and others are planned to reach still larger numbers of physicians in the community. The following states have held such institutes: West Virginia, Virginia, New Jersey, New York, Georgia.

At the Institute in Washington a special course in clinic nursing and social work was given for nurses. Sixty-seven nurses enrolled in this course which was conducted by Doctors Edward L. Keyes, Jr., Valeria H. Parker, and Rachelle Yarros, and Misses Ann Doyle and Henrietta Additon. The program was as follows:

*Clinic Nursing and Social Work*

1. The function of the venereal disease nurse and the social worker, Dr. Yarros
2. The functions of the nurse in the treatment of gonorrhea and syphilis .....Dr. Keyes
3. Dealing with the patient's family .....Dr. Parker
4. The part of the nurse and social worker in the diagnosis of syphilis and gonorrhea in the home.....Dr. Yarros
5. The larger work of the venereal disease nurse and social worker .....Miss Additon
6. Review

These programs especially designed for physicians and nurses formed, of course, but a portion of the entire series which included the various phases of venereal disease control work. Both physicians and nurses attended other courses showing their interest in gaining an understanding of the various aspects of the problem.

In response to a strong demand throughout the country among city and county health officers, physicians, nurses and others for institute work, the United States Public Health Service is in communication with the various State Boards of Health in regard to a series of one-week public health institutes to be conducted during 1921 and 1922 in approximately twenty-five geographical centers of the United States.

It was first proposed that these institutes deal exclusively with the problem of venereal disease control. Most of the State Boards of Health which have thus far expressed themselves, however, appear to favor a general public health institute with special emphasis upon the problem of venereal diseases.

It is the intention of the Public Health Service to secure the coop-



eration of leading specialists throughout the United States for these institutes and to maintain a high standard of academic excellence in all the lecture work.

The Public Health Service will be glad to send further information to those who are interested.

#### CLINIC FACILITIES

One of the greatest problems in dealing with venereal infections is the cost of efficient treatment. Both syphilis and gonorrhea must often be treated over long periods of time, and in the case of the former expensive drugs must be provided. The necessity therefore of securing facilities for treating patients who can pay but a small sum or who are unable to pay anything, becomes evident.

To meet this need the Public Health Service has emphasized as a most important phase of its medical program the establishment of a network of clinics throughout the United States, where treatment for venereal disease may be secured at nominal cost, or where free treatment can be obtained by those unable to pay.

As has been noted in other countries where free clinics have been put in operation, the number of cases treated at these clinics has in general showed a steady increase. In Rotterdam for instance where a clinic has been operating for seven years with no change in methods of operation, it has been found that the number of cases increased steadily for several years before the maximum was reached and then began to decline. As the clinics in this country have most of them not been in operation for three years yet, it is to be expected that the number of cases coming to the clinics for treatment would be still increasing and this, as a matter of fact, is the case in most instances.

Complete figures are, of course, not yet available for 1921, but the figures from the annual reports of 1919-1920 may be compared, and the increasing usefulness of the clinics demonstrated. In 1919 there were 237 clinics operating under the joint auspices of state boards of health and the U. S. Public Health Service, and 167 regularly reported their activities. Of the total number of clinics, 145 were established during the year 1919. In 1920 there were 427 clinics operating under state boards of health and the U. S. Public Health Service, and 383 clinics regularly reported their activities. One hundred and ninety of these clinics were established in 1920. It can be stated, therefore, that there was practically one hundred per cent increase

in clinic facilities throughout the United States during the past year. There was also one hundred per cent increase in clinic reporting.

Clinic reports show that twice as many patients received treatment in 1920 as in 1919. In 1920, 126,131 patients were admitted against 59,092 admitted in 1919, an increase as stated of over one hundred per cent.

Further than this the figures show that the treatment received by patients became progressively more efficient, for while 6,922 patients were discharged as noninfectious in 1919, 34,215 were discharged as noninfectious in 1920. Or, in other words, only one patient out of every three or four was discharged as noninfectious in 1920. However, as would be expected from the above, while the number of patients was doubled the number of treatments was tripled. In 1919, 8 treatments were given for each person admitted, while in 1920, 12.5 treatments were given for each patient, showing again greater efficiency in treatment.

Nearly three times as many Wassermann tests were made in 1920 as in 1919 (63,929 as against 175,872 in 1920) and nearly twice as many microscopic examinations for the gonococcus (89,419 against 155,275 in 1920), showing the laboratory facilities were being utilized more and more by physicians as well as in the clinics themselves.

State boards of health report 328,382 doses of arsphenamine distributed to physicians, hospitals, and clinics during 1920. Compared with last year's report, 118,055, this is an increase of 210,327 or 186 per cent.

The increase in the volume of work done was satisfactory and it was desired to make sure also of the quality of the work of the clinics. This was made possible through the Survey of Cities.

#### EFFICIENCY OF CLINICS

In February, 1919, the Public Health Service made a survey of cities in the United States with a population of 15,000 or more, in order to determine just what was being done in each of these cities to control venereal diseases. The cities to be surveyed were selected in accordance with the census estimate of 1917. This estimate showed a total of 467 cities with a population of over 15,000. At the time of the survey there were 427 clinics for the treatment of venereally diseased persons, but of this number only 359 were located in cities of more than 15,000 inhabitants. It should be remembered, therefore,

that the following statistics do not include all the venereal disease clinics in the United States, but refer only to clinics in cities of more than 15,000 inhabitants, according to the census estimate of 1917. The questions cover the following points:

Location of clinics; equipment; methods of sterilization; methods of case recording and history taking; personnel; methods of treatment; accessibility of laboratory facilities; days and hours open for treatment of patients; daily average attendance; per capita cost; average monthly cost of operation; methods used in increasing attendance, and fee charged, if any.

An ideal public health venereal disease clinic must have a convenient location preferably in some public building, where attendance will not be conspicuous. There must be facilities for diagnosis and for competent treatment for both gonorrhea and syphilis. The staff must be adequate for the clinic needs and for the necessary follow-up work. There must be day and evening hours, so that those employed can receive treatment, and there must be sufficient attendance to result in a reasonable per capita cost of treatment. Treatment must be free to those unable to pay.

The type of treatment given is, of course, all important in determining clinic efficiency. The survey showed that in 325 clinics, or 90 per cent, the treatment for gonorrhea was efficient, and that in 337 clinics, or 93 per cent, the treatment for syphilis was efficient. Three hundred clinics, or 84 per cent, had equipment which was considered entirely adequate.

Accurate diagnosis being essentially of prime importance, careful observations were made with regard to facilities for diagnosis. It was found that dark-field examinations could be carried out in 226 clinics (62.9 per cent); Wassermann tests could be made in 166 clinics (46.2 per cent); microscopic examinations for the gonococcus were being made in 202 clinics (56.2 per cent).

Out of 342 clinics reporting on hours, 198, or 57 per cent, had evening hours. Out of the 309 clinics reporting on attendance 175, or 58 per cent, had an average daily attendance of between 10 and 100 patients per day, and ten of these clinics averaged over 100 patients per day.

The per capita cost of treatment is an excellent way in which to judge the efficiency of a clinic from the standpoint of public health. In fifty clinics this averaged 50 cents or under, in 79 clinics it was



50 cents to one dollar, in 37 clinics it was one dollar to one dollar and a half, and in 20 clinics it was a dollar and a half to two dollars. The per capita cost of treatment was, therefore, under two dollars in 80 per cent of the clinics.

#### SCIENTIFIC RESEARCH

Scientific researches for the discovery of more effective medical measures in the prevention and treatment of venereal diseases have been carried out since July, 1918. These researches were made possible by allotments from the Interdepartmental Social Hygiene Board, the work being carried on by investigators in 22 different universities scattered through the United States. Many of these researches are still incomplete.<sup>1</sup>

#### II. PREVENTIVE MEASURES

It is, of course, not possible in the scope of this paper to go as fully into the preventive measures. These, however, should be briefly summarized in order to give an idea of the rounded program which is being carried out. Preventive measures include both the legal and educational phases of the program.

#### LEGISLATIVE ACTIVITIES

One of the duties of the legal section of the Division was to see that as many states as possible secured their share of the Chamberlain-Kahn fund. During the second year (July 1, 1919, to June 30, 1920) it was necessary for the state to appropriate an equal amount to do so. In both 1919 and 1920 forty-seven states qualified. At the present time Nevada has also signified her intention of adopting venereal disease control measures which will enable her to qualify so that all the states will shortly be cooperating. The District of Columbia, however, has not yet qualified. Further work of the legal division consists in fostering the passage of state laws and city ordinances having for their aim the control of venereal disease and in urging the enforcement of laws which have been so passed. No less than 40 states in 1919 passed legislation aimed at venereal disease control; in 1920 thirteen states did likewise. In 1919 there were 222 city ordinances of this character passed and in 1920 there were 102.

Model laws and ordinances that have been found serviceable have been drawn up and have been available to states and cities. In many

cases these forms have been followed in framing legislation. Such laws and ordinances include those prohibiting the use of taxicabs, dance halls, lodging houses, hotels, etc., for the purpose of prostitution. Others necessitate compulsory medical examinations and treatment for those arrested for sex-offences, and still others prohibit the sale and advertising of quack venereal disease remedies and nostrums. To aid the states in the suppression of commercialized prostitution, as the most important focus for spreading venereal disease, has throughout been the chief aim of the legal section.

#### EDUCATIONAL

Educational activities have as their aim to bring to the attention of the public the facts about venereal disease, their dangers and the necessity of securing prompt and efficient treatment, and also proper sex instruction of children by parents and teachers.

Sixty-three pamphlets on various phases of sex education, and hygiene and advice to those infected with venereal disease have been published, and extensively distributed. Framed placards giving advice to persons infected with venereal disease have been placed in railway cars and stations, and other public places and have been useful in inducing many persons to consult a reliable physician or to go to a clinic. Educational lectures have been given by physicians and other workers of the Public Health Service and state boards of health before societies and clubs which request their services. In 1919 there were more than eight thousand such lectures given; in 1920 there were 12,000, the average attendance being between 130 and 200 persons. Health exhibits and lantern slide showings are other features of this phase of the work. More than two thousand of these showings were given in 1919 and more than eleven thousand in 1920, the average attendance being between 200 and 250. Over one thousand educational motion picture showings were given in 1919, and over two thousand in 1920.

It is, of course, not possible to give an idea of the extent of the legal and educational activities of the Division in such a short statement.

#### PLANS FOR THE FUTURE

Although much has been accomplished during the time the Division has been in existence to limit venereal infections through edu-

educational, legal and medical means there still remains an immense amount of work to be done before it can be said that the venereal diseases have been brought under control.

At a meeting of certain Health Officers held in Washington, January 12, 1921, certain resolutions were adopted and later generally approved by State boards of health which map out clearly the phases to which it is felt advisable that energy should be directed, during the immediate future. Those of the resolutions which deal with medical measures are herewith appended as embodying the most needed developments in the field of venereal disease control.<sup>2</sup>

**RESOLVED:** That there is urgent need for all physicians to recognize their responsibility to the community and the patient in the control and the treatment of venereal disease, by themselves raising the standard of treatment. This implies that a physician who is unfamiliar with or unprepared to employ modern methods in the management of these diseases should not accept such cases for treatment but should refer them to some private or public physician who is properly equipped.

**RESOLVED:** That the venereal disease control movement cannot reach full effectiveness without the intelligent and sympathetic cooperation of the medical profession. This cooperation can best be obtained by:

1. The rapid extension of teaching facilities for medical students so that knowledge of the medical, social and public health aspects of these diseases may be taught by actual contact with patients in the clinic under the direction of qualified teachers.

2. By making available to all physicians by means of clinics, lectures, demonstrations, and institutes the most recent developments in medical and social knowledge of the venereal diseases.

3. By the development of state diagnostic facilities for the use of the practicing physician.

**RESOLVED:** That the development and maintenance of a competent medical personnel under executive leadership in the field of venereal disease control demands training whose duration and character is varied with the work for which preparation is sought; from six months for the routine performance of the technical work of treatment to three or more years for the preparation of men who are to assume the full medical and administrative responsibilities of the



expert. For the purpose of such training special postgraduate courses in association with medical schools and teaching centers providing liberal and accessible clinical material are essential. The development of such schools should be encouraged and active participation of their graduates in this work should be sought. The maintenance of an efficient personnel further requires the provision of inspiration and incentive to individual development and reward for initiative comprised in (a) adequate material equipment for laboratories and clinics; (b) adequate technical and medical assistance for the handling of routine work; (c) sufficient freedom from routine and provision of funds to make possible the conduct of research; (d) much more generous provision for the salary of personnel than is now the rule.

The continuance of public parsimony in this field will ultimately divert from the public service into more generously rewarded lines of activity those men whose training and capacity can redeem the work from mediocrity and the movement from futility.

**RESOLVED:** That the obligation of a public or private agency for the treatment of venereal disease does not end with the mere overcoming of a group of symptoms or the temporary control of contagiousness but should extend throughout the course of the disease. The fact that a person has a venereal disease should not as such act as a bar to his admission to any hospital or institution receiving public funds. The aim of all agencies for the care of venereal diseases should be to trace out infected individuals; to carry treatment to point of cure or arrest; to accumulate a body of records for the intelligent control of the individual case, and to further scientific research; to maintain a follow-up system and to provide special diagnostic facilities; careful and repeated observation and expert advice for the individual patient throughout life.

#### REFERENCES

- <sup>1</sup>Contributions to Medical Science Developed under the Auspices of the Interdepartmental Social Hygiene Board. Dr. Wm. F. Snow, *Am. Jour. of Tropical Med.*, April, 1921.
- <sup>2</sup>Public Health Activity and Private Practice in Venereal Disease Control. John H. Stokes. *Jour. Am. Med. Assn.*, April 30, 1921.

# EXPERIMENTAL OBSERVATIONS UPON THE EFFECT OF CHOLESTEREMIA ON THE RESULTS OF THE WASSERMANN TEST

BY CHARLES F. CRAIG, LIEUTENANT COLONEL, MEDICAL CORPS, U. S.  
ARMY, AND WILLIAM C. WILLIAMS, CAPTAIN, MEDICAL  
ADMINISTRATIVE CORPS, U. S. ARMY

*From the Division of Laboratories, Army Medical School, Washington, D.C.*

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A NUMBER of articles have recently appeared in the literature in which claims have been made that the presence of an increased amount of cholesterin in the blood will cause positive results with the Wassermann test and that such results may be obtained in nonsyphilitic individuals if a cholesterin reinforced antigen be used in the test. Henes, who believes that a hypercholesteremia has a very important effect upon the results obtained with this test, goes so far, in a recent contribution,<sup>1</sup> as to claim that the positive Wassermann reaction practically depends upon the amount of cholesterin in the blood and that in certain conditions, as pregnancy, where there may be present a hypercholesteremia, a positive result may be obtained in nonsyphilitic individuals.

The conception that cholesterin, when present in the blood in increased amounts, may give rise to a positive Wassermann reaction, has undoubtedly arisen because of the observations of Browning, Cruickshank and McKenzie,<sup>2</sup> Sachs,<sup>3</sup> McIntosh and Fields,<sup>4</sup> Walker and Swift<sup>5</sup> and others, that the alcoholic extracts of tissues used as antigen in the complement-fixation test for syphilis are rendered much more efficient if cholesterin be added to them. While this is true, there are very few students of the subject who believe that this fact indicates that the positive reaction with this test is due to cholesterin in the blood of the individual tested and all of our information regarding the nature of the reaction is opposed to such a conclusion.

Fraser and Gardner<sup>6</sup> have shown that in the animal body cholesterin originates chiefly from food, either as such in animal food, or from plants where it occurs in isomeric forms which the animal is

able to change into cholesterol. The greater portion of the cholesterol so obtained is excreted in the feces or by the skin after partial oxidation or reduction. Bloor and Knudson<sup>7</sup> state that in the intestine cholesterol occurs practically free while in the secretions of the skin it occurs almost entirely in the form of esters of the fatty acids. Robertson<sup>8</sup> states that the power of the body to destroy cholesterol is very limited and if a considerable excess is administered in the diet the unutilized cholesterol is stored in various tissues, particularly in the liver, spleen and suprarenal glands, and may lead to very serious results.

An increase in the amount of cholesterol in human blood serum, which normally varies only within narrow limits, has been claimed to occur, by several observers, in a number of disease conditions, but the evidence of such an increase is very conflicting and unsatisfactory, when critically examined. Gorham and Myers<sup>9</sup> found a hypercholesteremia in some cases of arteriosclerosis, nephritis, obstructive jaundice, diabetes, and in all anemias of the pernicious type and in the cachexia of malignancy. They did not find any increase in the amount of cholesterol present in the blood serum in syphilis and their findings in cholelithiasis were very inconstant. Luden<sup>10</sup> states that the cholesterol content of the blood is increased in pregnancy and lactation, diseases of the liver and malignant growths. Hermann and Neumann<sup>11</sup> and Albrecht and Weltmann<sup>12</sup> found an increase of cholesterol in the blood of pregnant women; Chauffard, Richet and Grignaut<sup>13</sup> in the blood in the late stages of typhoid fever; Henes<sup>14</sup> and Rothschild and Rosenthal<sup>15</sup> in cholelithiasis; and Fischl<sup>16</sup> in diseases of the skin not accompanied by fever, as urticaria, eczema and mycosis fungoides.

On the other hand, careful observers have failed to confirm these findings and in this respect the investigations of Denis<sup>17</sup> are of special value. From his observations, Denis concluded that the amount of cholesterol in the blood is not increased in nephritis, cardiorenal disease, cardiac disease, or arteriosclerosis and that there is no relation between the nonprotein nitrogen of the blood and the amount of cholesterol present. He failed to find any increase in the blood cholesterol in twelve cases of pregnancy, seven cases of typhoid fever, nine cases of cholelithiasis, fourteen cases of malignant disease, nine cases of pneumonia, five cases of cirrhosis of the liver, seventeen cases of eczema, two of mycosis fungoides, twelve cases



of pernicious anemia, eight cases of secondary anemia, and twelve cases of disease of the ductless glands. Denis found no increase in blood cholesterin in fourteen syphilitic infections and of twenty-five diabetics only five showed a slight increase in the blood serum cholesterin.

From this brief summary of the question it is evident that there is no agreement among investigators as to the occurrence of a hypercholesteremia in normal or diseased individuals. It is evident that if this condition occurred in such common conditions as pregnancy, diabetes, diseases of the liver, and nephritis, and that the presence of cholesterin in the blood in increased amounts produces a positive Wassermann test, the subject would be of the very greatest importance in the interpretation of the results of this test. Although the literature fails absolutely to show that the amount of cholesterin in the blood is increased in syphilitic infections the sweeping statements of Henes<sup>19</sup> that the positive result in the Wassermann test is largely due to the increased amount of cholesterin in the blood serum of syphilitics were thought worthy of careful investigation and we decided to determine, if possible, whether forced feeding with this substance and its consequent accumulation in the blood, would result in the production of a positive Wassermann reaction in an animal known to give such a reaction after infection with *Treponema pallidum*.

For this purpose the rabbit was selected both because this animal is known to give a positive Wassermann test after experimental infection with syphilis and because the feeding of large amounts of cholesterin to rabbits results in its accumulation in the blood, as shown by Rothschild<sup>20</sup> and Klotz.<sup>21</sup> In these animals there is a decided limit to the power of excretion of cholesterin when it is fed in large amounts and it accumulates at first in the blood and later in the spleen, liver and suprarenals; furthermore, that the effect of this accumulation of cholesterin is especially severe in rabbits is shown by the fact that it is deposited in large amounts in the intima of the arteries, causing the formation of atheromatous lesions similar to those observed in arteriosclerosis, a phenomenon not observed in experiments with this substance in any other species of animal. In view of the susceptibility of the rabbit to cholesterin poisoning, as shown by the serious nature of the lesions that have been studied, following its feeding in large amounts, and its accumulation in the blood, it was thought

that if cholesterolin had any effect upon the Wassermann test it should be evident after feeding experiments upon these animals.

In order to observe the effect of cholesteremia upon the Wassermann reaction when a cholesterolized antigen was used, ten rabbits were selected, five for the feeding experiments and five to act as controls. As we could not find any exact data in the literature upon the amount of cholesterolin it would be necessary to feed in order that an excess of cholesterolin should appear in the blood serum, we empirically selected a quantity equivalent to 1.25 grams per kilo of body weight of the rabbit experimented with.

The Wassermann reactions were all performed with an antihuman hemolytic system, using the technic of Craig,<sup>22</sup> the antigen consisting of an alcoholic extract of human heart to which 0.4 per cent cholesterolin was added.

Before the experiment all of the rabbits were kept under observation for ten days, the Wassermann test being made upon their blood every few days, and it was found consistently negative in all ten rabbits during this period. Prior to the commencement of the feeding experiments a cholesterolin determination was made upon the blood serum of all the animals and it appeared from these determinations that the normal cholesterolin limits in the blood of normal rabbits varied from 87.5 mgms. to 133 mgms. per 100 c.c. of blood serum.

The feeding was continued in the five rabbits selected for this purpose for a period of eighteen days and no difficulty was experienced in getting the animals to take the cholesterolin when it was well mixed with chopped carrots. No clinical symptoms were noted following the feeding of cholesterolin for this period of time except a slight loss in weight and this was probably due to the limitations of the diet during the feeding experiment.

The following protocols give the results of these feeding experiments as regards the amounts of cholesterolin in the blood and the results of the Wassermann tests.

RABBIT No. 1301. Four negative Wassermann reactions during period of preliminary observation.

Cholesterolin prior to feeding. 117.6 mgms., per 100 c.c. of blood serum.

Dose of cholesterolin administered daily: Four grams.

Ninth day of feeding: Cholesterolin, 180.3 mgms. per 100 c.c. of blood, an increase of 53 per cent. Wassermann test negative.

Eighteenth day of feeding: Cholesterin, 877.5 mgms. per 100 c.c. of blood serum, an increase of 654 per cent. Wassermann test negative.

Nineteenth day: Feeding stopped.

Thirtieth day: Cholesterin, 961.5 mgms. per 100 c.c. of blood serum, a further increase of 9.6 per cent. Wassermann test negative.

Total increase of cholesterin in blood serum, 663.6 per cent, with a consistently negative Wassermann reaction.

RABBIT No. 1302. Four negative Wassermann reactions during period of preliminary observation.

Cholesterin prior to feeding: 108.3 mgms. per 100 c.c. of blood serum.

Dose of cholesterin: Three grams daily.

Ninth day of feeding: Cholesterin, 311.9 mgms. per 100 c.c. of blood serum, an increase of 188 per cent. Wassermann test negative.

Eighteenth day of feeding: Cholesterin, 736.3 mgms. per 100 c.c. of blood serum, an increase of 680 per cent. Wassermann test negative.

Nineteenth day. Feeding stopped.

Thirtieth day: Cholesterin, 517 mgms. per 100 c.c. of blood serum, a decrease of 38.8 per cent from last determination. Wassermann test negative.

Highest increase of cholesterin in blood, 680 per cent, with a consistently negative Wassermann reaction.

RABBIT No. 1303. Four negative Wassermann tests during period of preliminary observation. Cholesterin, 133.8 mgms. per 100 c.c. blood serum. Dose of cholesterin, 2.6 grams per day.

Ninth day of feeding: Cholesterin, 195.5 mgms. per 100 c.c. of blood serum, an increase of 46 per cent. Wassermann test negative.

Eighteenth day of feeding: Cholesterin, 495 mgms. per 100 c.c. of serum, an increase of 270 per cent. Wassermann test, negative.

Nineteenth day: Feeding stopped.

Thirtieth day: Cholesterin, 565.6 mgms. per 100 c.c. of blood serum, a further increase of 14.3 per cent. Wassermann test negative.

Highest percentage of increase of cholesterin, 284.3 per cent, with a consistently negative Wassermann reaction.

RABBIT No. 1304. Four negative Wassermann reactions during period of preliminary observation. Cholesterin prior to feeding: 119.6 mgms. per 100 c.c. of blood serum. Dose of cholesterin, 2.6 grams per day.

Ninth day of feeding: Cholesterin, 243.9 mgms. per 100 c.c. of blood serum, an increase of 104 per cent. Wassermann test negative.

Eighteenth day of feeding: Cholesterin, 793.5 mgms. per 100 c.c. of blood serum, an increase of 563 per cent. Wassermann test negative.

Nineteenth day. Feeding stopped.

Thirtieth day. Cholesterin, 266 mgms. per 100 c.c. of blood serum, a decrease of 66.5 per cent since last determination. Wassermann test negative.

Highest percentage of increase of cholesterin in blood, 563 per cent, with a consistently negative Wassermann reaction.

RABBIT No. 1305. Four negative Wassermann reactions during the period of preliminary observation.



Cholesterin prior to feeding: 103.3 mgms. per 100 c.c. of blood serum.

Dose of cholesterin, 2.8 grams per day.

Ninth day of feeding: Cholesterin, 216.8 mgms. per 100 c.c. of blood serum, an increase of 110 per cent. Wassermann test negative.

Tenth day of feeding. Animal died from "snuffles."

No atheromatous changes were observed in arteries, nor could any other pathologic lesions due to cholesterin be detected.

Highest increase in cholesterin in the blood, 110 per cent, with a negative Wassermann reaction.

#### CONTROL RABBITS

RABBIT No. 1306. Four negative Wassermann reactions during period of preliminary observation. Kept under same conditions as other normal animals in animal room.

Cholesterin prior to experiments: 107.6 mgms. per 100 c.c. of blood.

Wassermann reactions negative on the 9th, 18th and 30th days.

Cholesterin on 30th day, 113.6 mgms. per 100 c.c. of blood serum, probably within the range of normal variation.

RABBIT No. 1307. Four negative Wassermann reactions during period of preliminary observation. Kept under same conditions as other normal animals in animal room.

Cholesterin prior to experiments, 130.9 mgms. per 100 c.c. of blood serum.

Wassermann reactions negative on the 9th, 18th and 30th days.

Cholesterin on 30th day 103.2 mgms. per 100 c.c. of blood serum, probably within the range of normal variation.

RABBIT No. 1308. Four negative Wassermann reactions during period of preliminary observation.

Cholesterin content of blood prior to experiments, 88.3 mgms. per 100 c.c. of blood serum.

Wassermann reactions negative on the 9th, 18th, and 30th days.

Cholesterin content on 30th day, 110.6 mgms. per 100 c.c. of blood serum, probably within the normal variation range.

RABBIT No. 1309. Four negative Wassermann reactions during the period of preliminary observation.

Cholesterin content of blood prior to experiments, 87.5 mgms. per 100 c.c. of blood serum.

Wassermann reactions negative on 9th, 18th and 30th days.

Cholesterin content on 30th day, 106.8 mgms. per 100 c.c. of blood serum, probably within the range of normal variation.

RABBIT No. 1310. Four negative Wassermann reactions during period of preliminary observation.

Cholesterin content prior to experiments, 89.5 mgms. per 100 c.c. of blood serum.

Wassermann reactions negative on the 9th, 18th and 30th days.

Cholesterin content of blood on 30th day, 114.7 mgms. per 100 c.c. of blood serum, an increase of 25.2 mgms. per 100 c.c. of blood serum, probably within the range of normal variation.

A careful study of the protocols given demonstrates that the five rabbits used in the feeding experiment showed an enormous in-

crease of cholesterin in the blood serum during the time that they were being fed. This increase ranged as high as 680 per cent in one of the animals. Table I gives in detail the increase in cholesterin noted during the experiments.

TABLE I

CHOLESTERIN CONTENT OF BLOOD EXPRESSED IN MGMS. PER 100 C.C. OF SERUM					
Rabbit No.	Prior to feeding	9th day of feeding	18th day of feeding	Feeding discontinued on 18th day	30th day. 12 days after cessation of feeding
1301	117.6	180.3	877.5		961.5
1302	108.2	311.9	844.5		517.
1303	133.8	195.5	495.		565.6
1304	119.6	243.9	793.5		266.
1305	103.3	216.8	Died on 10th day		

Despite the great increase in the cholesterin content of the blood in these animals, a greater increase than would ever be observed in the human being in health or in disease, the blood serum gave absolutely negative Wassermann reactions upon the 9th, 18th and 30th days of the experiment and in not a single instance was there the slightest trace of inhibition of hemolysis in any of the tests that were made.

The control rabbits, which were kept and fed under the same conditions as other normal rabbits in the laboratory, showed considerable variation in the cholesterin content of their blood during the period of the experiments. The greatest variation was an increase of 25.2 mgms per 100 c.c. of serum on the 30th day, in Rabbit No. 1310, during which period the animal gained 240 grams in weight. This variation is undoubtedly within the range of normal variation and can in no way be compared with the great increase of 843.9 mgms. per 100 c.c. of blood serum, which occurred in Rabbit No. 1301, for example. The experiments are confirmatory of those of other observers in proving that in the rabbit the feeding of large amounts of cholesterin results in the accumulation of relatively enormous amounts of this substance in the blood.

An interesting observation, which demonstrates that this accumulation of cholesterin in the blood continues for some time after the

feeding of the substance is stopped, was noted in two of the rabbits, the cholesterolin content of the blood increasing for as long as 12 days after the feeding of cholesterolin had ceased. In one of these animals the increase amounted to 14.3 per cent and in the other to 9.6 per cent. In the other two rabbits rapid decreases occurred after the feeding was stopped, amounting to 38.8 and 66.5 per cent respectively.

#### DISCUSSION

It is evident that the results of these experiments demonstrate that increased amounts of cholesterolin in the blood of rabbits cannot cause a positive Wassermann reaction and that the presence of cholesterolin in the blood, even in amounts so enormous as never to be encountered in man, have no inhibitory effect upon hemolysis. It is, we believe, justifiable to conclude that the same results would be obtained if the feeding of cholesterolin in large amounts to man had been followed, especially in view of the results of the observations of Weston<sup>23</sup> and of Stein,<sup>24</sup> who have definitely shown that the amount of cholesterolin in the blood of syphilitics has no effect upon the strength of the Wassermann reaction. Weston examined seventy-five sera, twenty-five from normal and fifty from insane individuals. Of the latter twenty-five gave a positive Wassermann reaction and twenty-five a negative reaction. The positive cases were either latent infections or paretics. He found that the cholesterolin content of the blood serum in these individuals bore no constant relation to the results of the Wassermann test and that the cholesterolin content of the blood of the insane did not differ appreciably from that of normal individuals. Stein tested thirty-six cases of syphilis of less than three years' duration and thirty-three of more than three years' duration and demonstrated that there was no relation between the amount of cholesterolin present in the blood serum and the character of the Wassermann reaction. In fact, Stein found that in many cases giving a negative Wassermann reaction the cholesterolin content of the blood serum was greater than in those giving a positive reaction.

In view of our results upon the feeding of cholesterolin to rabbits and those of the investigators mentioned, we believe that the amount of cholesterolin in the blood bears no relation to the production of a positive Wassermann reaction and that the cholesterolin in the blood serum is not the cause of such a reaction. The most recent in-



vestigations as to the exact nature of the positive Wassermann reaction indicate that the substance in the syphilitic blood serum which causes a positive result is related to the globulins, which are known to be increased in the blood and spinal fluid in syphilis, especially the euglobulin.

#### CONCLUSIONS

1. The feeding of 1.25 grams of cholesterin per kilo of body weight to rabbits results in an enormous accumulation of cholesterin in the blood, an accumulation that persists, in some instances, for several days after the feeding is stopped.

2. The hypercholesteremia produced by feeding rabbits large amounts of cholesterin does not cause the blood serum of these animals to give a positive Wassermann reaction.

3. There is no relationship between the cholesterin content of the blood serum of rabbits and the results of the Wassermann test, all of the animals experimented upon giving a consistently negative reaction despite the enormous increase in the cholesterin content of their blood serum resulting from the feeding of this substance.

We are indebted to Major S. A. White, Medical Corps, U. S. Army, for the chemical work in connection with the cholesterin determinations.

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## VIABILITY OF SPIROCHETE PALLIDA IN EXCISED TISSUE AND AUTOPSY MATERIAL

BY GEORGE R. LACY, M.D., AND SAMUEL R. HAYTHORN, M.D.,  
PITTSBURGH, PA.

*From the Wm. H. Singer Memorial Research Laboratory*

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OUR interest in the occurrence of the Spirochete pallida in dead tissues was aroused some months ago by finding actively motile spirochete in the blebs and organs of a stillborn congenitally syphilitic infant which had been kept in the refrigerator twenty-six hours prior to autopsy. The organisms were so numerous in the serum from the lungs and the superficial blebs and were so actively motile that rabbits were inoculated intratesticularly and typical syphilitic lesions developed. Although the danger of syphilitic infections from postmortem material have been commonly denied, the demonstration of actively motile virulent Spirochete pallida in dead tissue shows definitely that such infections are possible.

On referring to the literature one is impressed with the relatively small amount of actual knowledge which exists on the occurrence of the spirochete outside the body. Innocently acquired syphilis and extragenital primary sores are common enough to be very important factors from a sanitary standpoint. Buckley<sup>1</sup> in "Syphilis of the Innocent" and Vedder<sup>2</sup> in "Syphilis and Public Health" have given excellent résumés of the subject. In a series of more than 20,000 extragenital infections with syphilis the majority have been acquired through direct contact with syphilitic patients. Kissing, wet nursing, and handling of syphilitic patients by doctors and nurses have been the more common modes of infection. Several hundred cases of infection have been reported following minor operations, such as circumcision, cupping, tattooing, and the arm to arm method of vaccination as practiced in the preserum days. Cases have also been reported as having developed from the use of contaminated drinking cups and other utensils used by syphilitic persons. All of these instances emphasize the necessity of a more complete knowl-

edge of the viability of the *Spirochete pallida* outside of living tissue.

Several pieces of work have been carried out in this direction. The researches of Hartmanni<sup>3</sup> showed the spirochete lost its motility as soon as drying occurred and that on resuspending the dried material in physiologic salt solution its motility did not return. His work was not controlled by animal inoculations. The work of Neisser,<sup>4</sup> however, showed that material that had been capable of producing syphilis in monkeys was unable to produce it after the fluid containing the spirochete had been dried. Gastou and Comandon<sup>5</sup> investigated the length of time that spirochete could be found on drinking glasses used by syphilitics at ordinary drinking fountains. Patients with mucous patches or chancres of the lip were selected as subjects and the glasses, after use, were dipped in water in the customary manner employed for washing such glasses at public houses. On examination, it was found that the mouth secretions remaining on the glasses contained active spirochete as long as thirty minutes after inoculation. Neisser,<sup>4</sup> Landsteiner,<sup>6</sup> and others working independently also found that infectious material lost its power of producing syphilitic lesions after having been exposed to the following temperatures: (1) Three hours at 10° C.; (2) 24 hours in the ice chest; and (3) 30 minutes at 48° C. Bronfenbrenner and Noguchi's<sup>7</sup> experiments showed that in saline suspensions *Spirochete pallida* were killed in 7 to 10 minutes at 45° C. Zinsser and Hopkins<sup>8</sup> working with cultures of spirochete exposed their cultures to diffuse light of the laboratory at 22° to 25° and found that in a moist condition the spirochete lived as long as 11½ hours, but that when dried on cover slips they rapidly died. From their article it is questionable whether or not they obtained a growth after complete drying of the cover slips.

Our experiments have been conducted in an effort to determine the time during which the *Spirochete pallida* remain alive in dead tissues, the criteria being the motility of the organism and its ability to transmit the disease to a new host. The question of saprophytic growth and of the optimum temperature for maintaining motility are allied problems which have arisen and have been investigated during the course of the work.

The materials used in the work were obtained from an infant



dead of congenital syphilis, excised chancres, and serum collected from primary sores of cases applying to the genitourinary clinic. The capillary pipette method of collecting serum from the suspected lesions was found most useful and was carried out as follows: The sore was cleansed with normal saline solution, the surface slightly abraded by gentle scarification with a gauze pack and the serum which oozed out was then taken up in a fine capillary pipette or Wright's tube. Several large drops could be obtained in this way and when it was desired the tube was sealed off in the flame and the serum preserved for future examination. Portions of the above-mentioned materials were stored in the refrigerator at 2° to 4° C. while other portions were kept at room temperature. The fluids used were kept in sealed tubes and the tissues either in sterile Petri dishes or tightly stoppered bottles. No preservative of any kind was used.

*Motility.*—The motility tests on serum specimens were taken after the contents of the capillary tube had been thoroughly mixed, so that the sample was a representative one. The tissues were prepared by emulsifying a small piece in normal saline solution and dark-field examinations made on the saline suspensions thus obtained. During the first forty-eight hours the organisms remained practically as motile as when first examined. After this time, there was a gradual diminution in the activity which became more marked as time advanced. The examinations were made first with a high dry lens and then with the oil immersion lens. The reason for this was that the *Spirochete pallida* were much more readily located with the high dry, and sluggish motility was more easily detected with oil immersion.

Positive motility was observed:

In human autopsy material 48 hours after death, the body having been kept in the refrigerator during this period;

In chancre, seven days after excision;

In serum exudate from chancre in sealed capillary tubes at room temperature, 121 days after collection;

In saline suspension of rabbit's testicle in sealed capillary tubes at room temperature, 58 days after castration;

In rabbit testicle at refrigerator temperature, 58 days after castration.

The motility of the spirochete was preserved in the tubes equally well at room and refrigerator temperatures.

#### ANIMAL INOCULATIONS

The animals used for testing the virulence of spirochete were rabbits and guinea pigs. The suspensions for injections were prepared in a manner similar to that used in making dark-field examinations. The dried materials used were prepared by dipping clean scalpels into serum containing large numbers of spirochete and allowing these scalpels to dry for varying lengths of time before using them to inoculate animals. Inoculations were made in all cases, except three, intratesticularly. In the three exceptions, inoculations were made into the vaginal mucous membrane. The animals were observed closely and at first appearance of a palpable mass, a dark-field examination was made.

The method of obtaining material for examination was to inject sterile normal saline solution into the testicle, produce a slight amount of trauma by moving the needle about in the tissues, and then aspirating some of the injected solution. In the positive cases this fluid usually contained numerous spirochete. As a rule the injection of the saline did not interfere with the course of the infection, but occasionally it would cause an older lesion to flare up and produce an acute diffuse orchitis. The character of the lesions was usually a circumscribed indurated nodule, less commonly a diffuse interstitial orchitis. In two instances there were skin lesions in addition to the orchitis.

We have divided our experimental animals into five groups.

Group I was composed of rabbits which were inoculated intratesticularly with syphilitic material from autopsy and from other rabbits during the first 26 hours after death or after operation. See Table I.

Group II was composed of 3 female rabbits inoculated in the vaginal mucous membrane with fluid from a chancre. The fluid contained a heavy suspension of spirochete. The results were all negative.

Group III the rabbits were inoculated intratesticularly with scalpels which had previously been dipped into heavy suspensions of

TABLE No. I

NO.	MATERIAL USED	SITE	RESULT	INCUBATION PERIOD	CHARACTER OF LESION
R. 1	Bleb and Lung Cont. of Baby H. 26 hours P. M.	L. T.	+	L- 49 days R-100 "	Indurated nodule and diffuse orchitis
R. 2	"	B. T.	+	83 "	Indurated nodule
R. 3	Fl. L. T. Rab. #1	B. T.	+	34 "	Spontaneous cure Dermatitis and Indurated nodule
R. 4	Susp. L. T. Rab. #1	L. T.	+	43 "	Atrophy and indurated nodule
R. 8	Fl. L. T. Rab. #4	L. T.	+	30 "	Indurated nodule, typical chancre and lesion on face
R. 10	Susp. R. T. Rab. #1	B. T.	+	App. 40 "	Diffuse swelling and in- duration
R. 11	Fl. L. T. Rab. #4	L. T.	+	36 "	Diffuse Hyp. & Ind. of B. T.
R. 24	Fl. L. T. Rab. #2	R. T.	+	36 "	1 skin lesion on L. T.
	Susp. L. T. R. 8	R. T.	+	29 "	Diffuse induration

A. E. = After Excision.

B. T. = Both Testicles.  
L. T. = Left Testicle.

R. T. = Right Testicle.

spirochete from a chancre. The scalpels were allowed to dry for periods ranging from 30 minutes to 54 hours. The skin and tunica vaginalis were incised with sterile scalpels and the infected scalpels were stuck into the testicle in an attempt to produce an infection. See Table II.

TABLE No. II

NO.	MATERIAL USED	SITE	RESULT	INCUBATION PERIOD	CHARACTER OF LESION
R. 12	Inf. Scalpel Dry for 30 min.	B. T.	-	-	-
R. 15	Inf. Scalpel Dry for 6 hrs.	B. T.	-	-	-
R. 18	Inf. Scalpel Dry for 24 hrs.	B. T.	-	-	-
R. 21	Inf. Scalpel Dry for 54 hrs.	B. T.	-	-	-

Group IV was composed of rabbits inoculated intratesticularly with suspensions of spirochete from a chancre and from syphilitic testicles at periods ranging from 1 hour to 20 days after operation. During this time the spirochete retained a moderate degree of motility. See Table III.



TABLE NO. III

NO.	MATERIAL USED	SITE	RESULT	INCUBATION PERIOD	CHARACTER OF LESION
R. 13	Susp. Chancre 1 hr. A. E.	B. T.	+	30 days	Indurated Nodule
R. 14	"	L. T. & Skin	+	11 days	Diffuse Induration
R. 16	Susp. Chancre 24 hrs. A. E.	B. T.	-	—	—
R. 17	"	B. T.	+ ?	29 days	Interstitial Orchitis
R. 19	Susp. Chancre 54 hrs. A. E.	B. T.	-	—	—
R. 20	"	B. T.	-	—	—
R. 22	Piece Chancre 7 days A. E.	L. T.	-	—	—
R. 23	Susp. L. T. R. 11 20 days after Cast	L. T.	-	—	—

Group V was composed of guinea pigs. Each pig was injected with fresh, actively motile, virulent spirochete, similar quantities of which produced infections in rabbits. The results in this group were all negative.

From a study of the tables, it will be observed that we were successful in producing experimental syphilitic lesions in the testicles of rabbits with the following materials:

Syphilitic autopsy material, twenty-six hours after death.

Chancre, twenty-four hours after excision.

Emulsified testicle of syphilitic rabbit, twenty-four hours after castration.

After complete drying of the spirochete, the inoculations were uniformly negative.

#### QUESTION OF SAPROPHYTIC GROWTH

From time to time we have taken small bits of tissue from syphilitic material and have stained them by the acetone-silver impregnation method in an attempt to determine whether or not there was a change in the relative number of spirochete present. In two instances, one specimen removed from a piece of testicle, and the other from a secondary lesion of a rabbit's face, we found many more spirochete present after thirty-six days than we had been able to demonstrate in the tissue when freshly removed at operation. Whether there was an actual increase in the number of organisms,

or whether bits of tissue containing greater numbers of spirochete were selected for the latter examination is not certain, but this finding coupled with retained motility seems to warrant further research to determine whether or not the spirochete are capable of growth as saprophytes in animal tissues.

We also took pieces of tissue containing spirochete and imbedded them in freshly removed testicles, placed them in the refrigerator and examined them after fifteen days. The original pieces and the apposed surfaces of the surrounding testicle were examined by the dark-field method and were found to contain motile spirochete, but silver preparations did not show that any spirochete had penetrated into the excised testicle.

It is probable, therefore, that the organisms were left there from contact and not from growth.

#### INVOLUTION

The study of sections of silver impregnated tissues kept for a considerable length of time before fixation, indicated that the spirochete lost their abrupt angular curves and tended to assume loose spiral forms. This tendency toward involution forms appeared to be more marked as the length of time was increased.

#### SUMMARY

From the experiments which we have carried out, it is evident that spirochete kept in serum or moist tissue, either human or animal, may retain slight motility as long as three months or more. Reliable dark-field examinations can be made on tissues or fluids collected several hours previously, provided they are kept moist and cool. Our work which is in accord with that of Neisser, would indicate that complete drying is probably fatal to the *Spirochete pallida*, since each of our rabbits inoculated with dried spirochete on scalpels, failed to develop syphilitic lesions. *Spirochete pallida* may, and in our case did, remain virulent in autopsy material for twenty-six hours or longer.

We are indebted to Dr. James C. Burt for the material received from the Genito-Urinary Clinic.

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## A CASE OF SYPHILIS OF THE PROSTATE

BY ALDRED SCOTT WARTHIN, M.D., PH.D., ANN ARBOR, MICH.

*From the Pathological Laboratory of the University of Michigan, Ann Arbor.*

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IN 1918, a survey of the literature of prostatic syphilis was made by Thompson<sup>1</sup>. He could find only 24 cases of supposed syphilis of the prostate recorded, and of these he accepts only 12 as authentic. The diagnosis in these 12 cases was made upon purely clinical grounds alone, with the exception of one case (Observation XIX, Warthin, 1918) in which the diagnosis was based upon the occurrence of characteristic tissue changes associated with the presence of typical spirochetes of syphilis. This is, therefore, the only positively demonstrated case of syphilis of the prostate existing in the literature at the present time, the writer in a thorough search having failed to add any other. Inasmuch as Thompson's abstract of this case consisted only of a brief quotation from the Harvey Lecture on "The New Pathology of Syphilis"<sup>2</sup>, in which the main features of the case were barely mentioned it would seem advisable, because of the importance of the case, to present it with more complete details. That this is justified is shown further by the great interest taken in the case, as evidenced by many inquiries received concerning it. The present report is therefore, made solely to place it on record in a complete form.

### CLINICAL HISTORY

Young white male, said to be 19 years of age, fell or jumped from a moving street-car striking squarely upon his head on the pavement. He was taken in an unconscious condition to the University hospital and admitted to Dr. de Nançrède's clinic, March 22, 1917. While being prepared for operation he died. Autopsy ordered by Coroner. The only facts of importance brought out concerning the previous history of the deceased was that he had acquired syphilis some two years previous and had been under recent treatment with mercury and iodides for some time.

## GROSS PATHOLOGY

Young male body of large build, 183 cm. long, bones heavy. Appeared older than reported age of 19. Over left shin, on right side of chest, and on left side of head numerous scars of healed syphilitic lesions. Fresh abrasion of right knee. Hematoma of left side of head extending down into neck. No fracture of skull cap. Meninges unusually adherent and thickened. Intrameningeal hemorrhage over right frontal lobe. Larger clot over the left parietal and occipital regions. At base of brain a large blood-clot extending to the posterior border of the foramen magnum. In the floor of the skull a T-shaped fracture beginning to the right of the midline posteriorly to the foramen and extending to the left, across the groove of the left lateral sinus where it met the cross of the T, one branch extending 8 cm. to the left, the other 6 cm. to the right across the floor of skull. Left middle ear was filled with blood. Multiple hemorrhages were found throughout the brain substance.

Main incision showed no pathologic conditions, except a persistent thymus.

Examination of heart and lungs revealed no gross pathologic changes, save a sclerotic patch on the anterior surface of right ventricle.

Spleen was large; very soft; follicles large.

Liver much enlarged, five finger-breadths below edge of ribs in the right nipple line. Capsule smooth except in region of gall bladder. Nothing notable on section. There were many adhesions between the gall bladder, pylorus, colon and duodenum. No stones in gall bladder. Adrenals smaller than normal. Kidneys were of normal size, and presented no abnormalities on section. Other organs also negative. The retroperitoneal lymph nodes were hyperplastic.

The prostate was of normal size and appearance, and on section presented to the eye no pathologic changes. The testes on section appeared to be normal.

## MICROSCOPIC PATHOLOGY

Evidences of active syphilis were found in the meninges, lungs, liver, adrenals, prostate and testes, in the form of diffuse or circumscribed plasma-cell infiltrations, often perivascular, with proliferation of blood vessels and fibroblastic tissue, often appearing as miliary vascular granulomas (gummas), showing no caseation, and with oc-

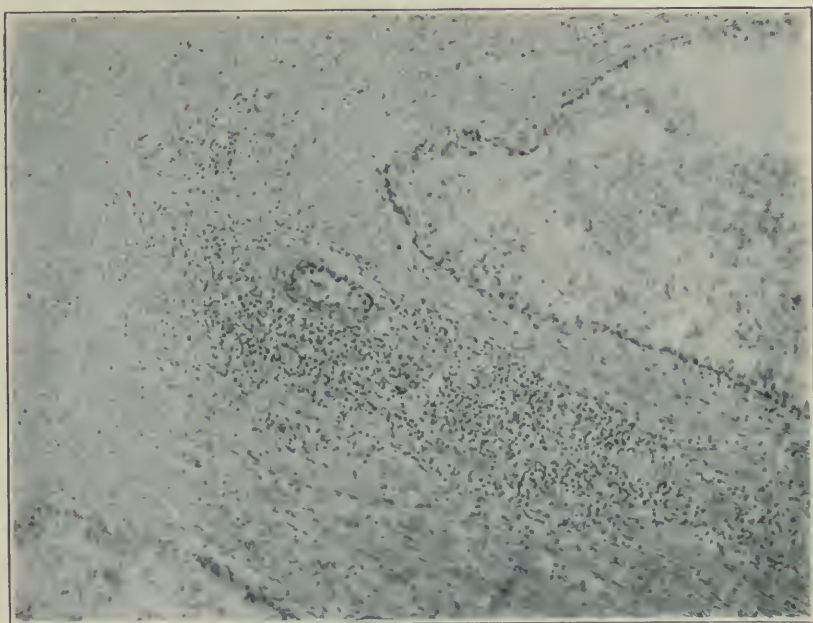


Fig. 1.—Syphilis of the prostate. Plasma-cell infiltrations of stroma, along the smaller vessels.

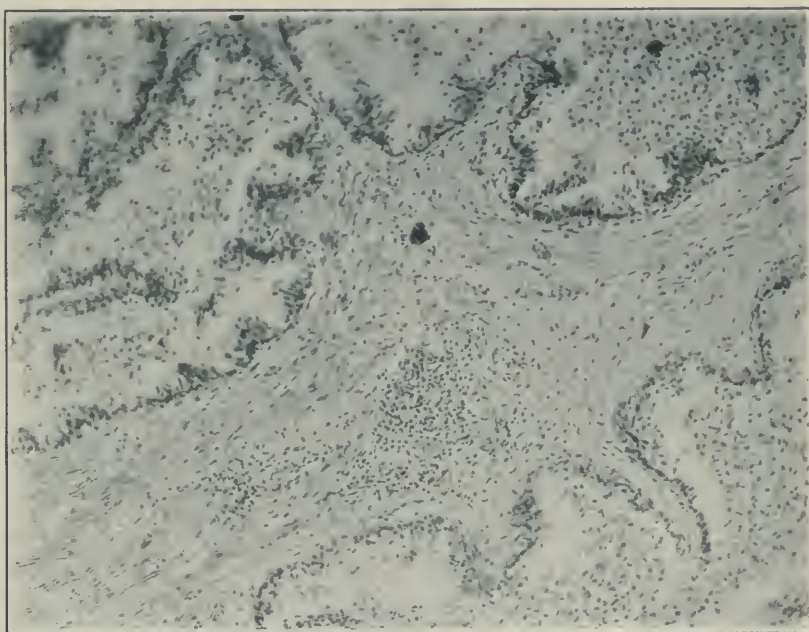


Fig. 2.—Syphilis of the prostate. Infiltrations of plasma-cells around the small vessels in the stroma. These infiltrations are characteristic in that they are not subepithelial as in chronic prostatitis of different etiology.





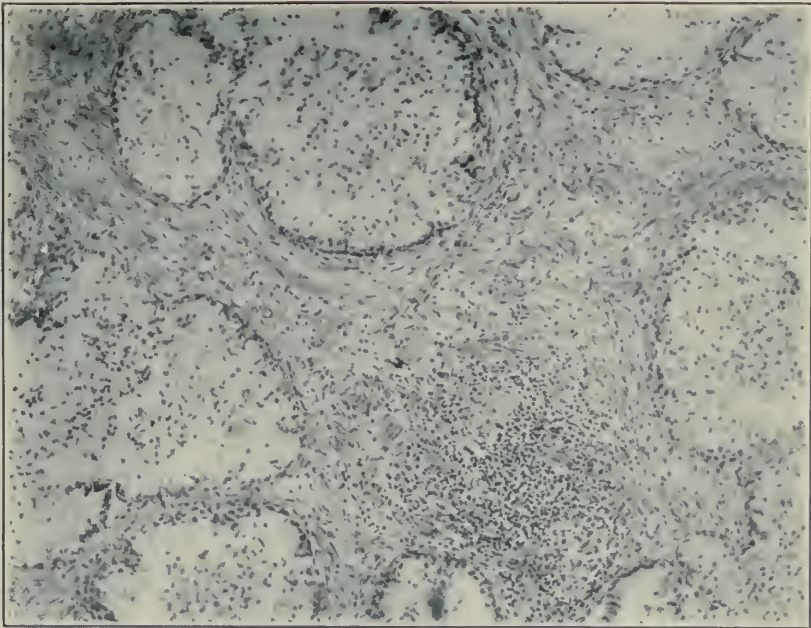


Fig. 3.—Syphilis of the prostate. Plasma-cell infiltrations of the stroma.

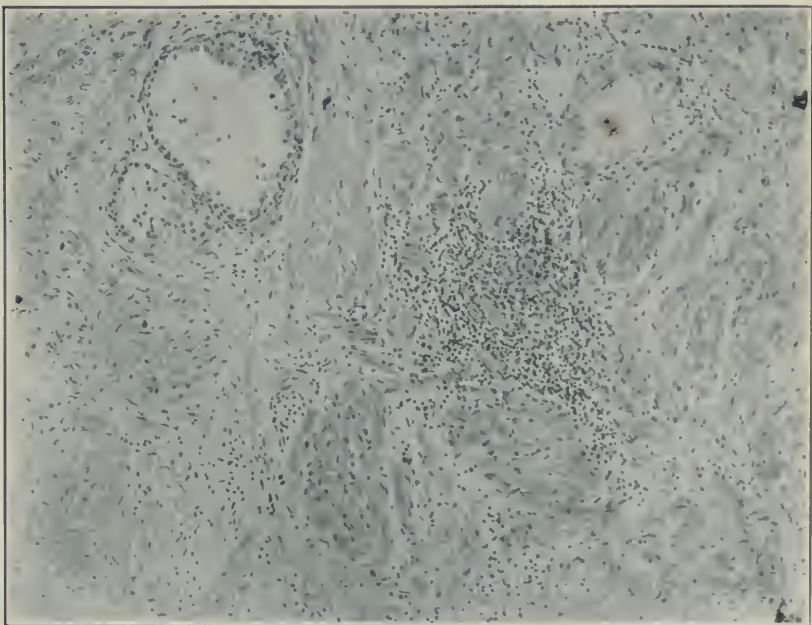


Fig. 4—Syphilis of the prostate. Small miliary gumma, perivascular plasma-cell infiltrations, in prostatic muscle-bundles.





casional giant cells. No tubercles were found in lungs, bronchial nodes or elsewhere. All lymph nodes were hyperplastic; the thymus showed abundant thymic structures; the spleen showed hyperplasia of stroma and lymphoid tissue with exhaustion of the follicles. The adrenals were hypoplastic. The testes showed an interstitial orchitis, with thickening of the basement membrane, plasma cell infiltrations and diminished spermatogenesis, some areas presenting a more advanced picture of syphilitic orchitis.

Multiple hemorrhages were found throughout the brain and in the meninges.

The prostate showed no glandular hyperplasia; the glandular spaces, on the contrary, seemed smaller and less numerous than in the adult prostate, the stroma being greatly in excess. Throughout the stroma there were plasma-cell infiltrations, either diffuse or more circumscribed. These infiltrations followed the capillaries or small veins, and the larger ones were distinctly perivascular, around groups of newly-formed blood vessels, and associated with a definite fibroblastic proliferation of the stroma, with occasional formation of giant cells of the foreign body type. These larger infiltrations and vascular proliferations appeared as miliary granulomas, of the type histologically of miliary gummas. No tendency to caseation was shown; on the contrary, some of the lesions showed thickening and obliteration of the blood vessels with resulting fibrosis. A striking feature of the plasma-cell infiltrations lay in the fact that they do not occur in close relationship to the gland spaces as in other forms of prostatitis, particularly the gonorrheal. The infiltrations are more diffuse and irregular, lie chiefly about half-way between the glands, are distinctly perivascular and not subepithelial. The cells are plasma cells rather than lymphocytes and are not aggregated into germ-centers, as is so frequently the case in chronic gonorrheal prostatitis. They are further characterized by a tendency to new formation of capillaries and an increase of the stroma. In general the prostatic lesions are precisely similar to those produced by syphilis in other organs, (heart, aorta, adrenals, pancreas, etc.). They are remarkable in this case for their degree and extent. They represent a more active process than those of an older latent syphilis.

In these active lesions small groups of typical *Spirochete pallida* were demonstrated by the Levaditi method. There is, therefore, no doubt that they are syphilitic in nature, and their occurrence in this

case demonstrates that the prostate may show the same involvement in syphilis that has been demonstrated for so many other organs and tissues of the body. They differ in no wise from the lesions found in the liver, adrenals and testes of the same case.

This case presents a much earlier stage of syphilis than is usually found at autopsy, and in a younger body, the stage of infection probably dating two years from the initial lesion. It is interesting to note that in this case the heart and aorta showed no syphilitic changes, while the liver, adrenals, prostate and testes showed the greater degree of involvement. The meningeal changes, the hyperplasia of the spleen and lymph nodes, and the pulmonary lesions are probably also the result of the syphilitic infection; although the individual was undoubtedly of the lymphatic type of constitution. The adrenal hypoplasia is to be taken as an evidence of the latter condition.

Although microscopically the prostate showed this picture of extensive infiltrations throughout the stroma, it presented no gross changes, and was of average normal size. That there could have been any clinical symptoms of prostatic involvement seems more than doubtful. The patient had made no complaint of any symptoms connected with his sexual tract, and was known to be actively sexually immoral. His antisyphilitic treatment had apparently been directed against the cutaneous lesions alone. As far as the prostatic lesions are concerned they constitute purely an accidental finding in a routine autopsy examination.

Whether such lesions in the prostate are common in the earlier active stages of syphilis we cannot say until some one makes systematic search for them. As to the prostates of older, more latent, cases of syphilis the occurrence of lesions so marked and so distinctively syphilitic in character as these has not fallen within the range of my experience, although I have examined the prostates of several hundred of such cases. The poverty of the literature speaks the same for other observers. Nevertheless, prostatic hyperplasia and fibrosis occur very frequently in such cases, but without any microscopic changes so characteristic of syphilis as in this young man. Small lymphocytic and plasma-cell infiltrations occur in some of the older cases, with localized areas of sclerotic, small, and apparently new-formed, vessels. It remains to be shown that these have anything to do with the coincident syphilis, or are a part of an associated chronic prostatitis due to other infection. The latter condition re-



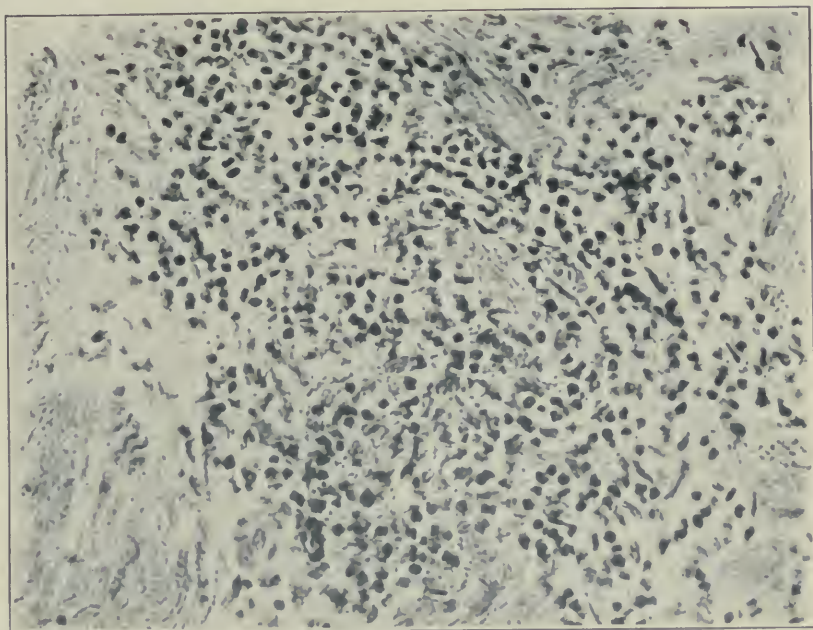


Fig. 5.—Syphilis of the prostate. High power view of small miliary gumma seen in Fig. 4. Plasma-cell infiltrations around new-formed capillaries.

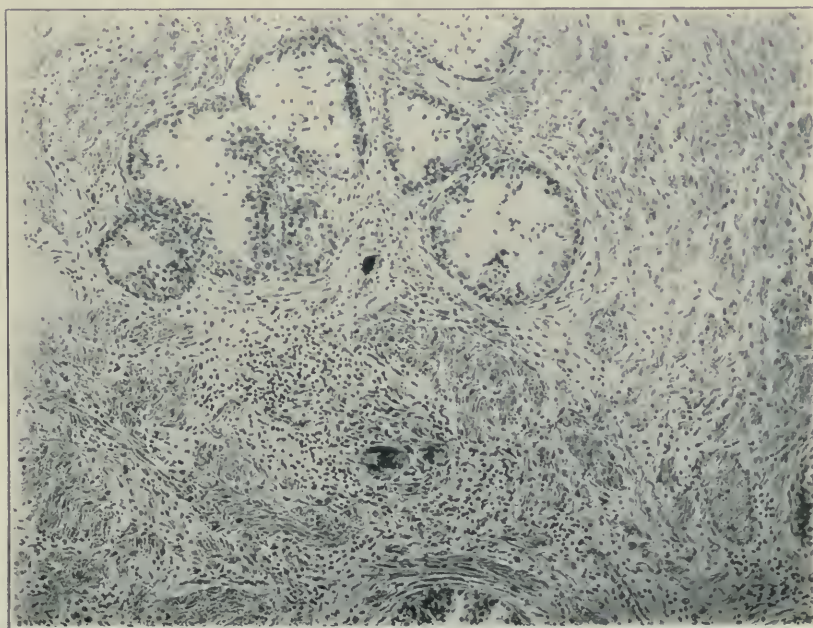


Fig. 6.—Syphilis of the prostate. Small miliary gumma with giant-cells. Spirochete pallida was found in sections from this.





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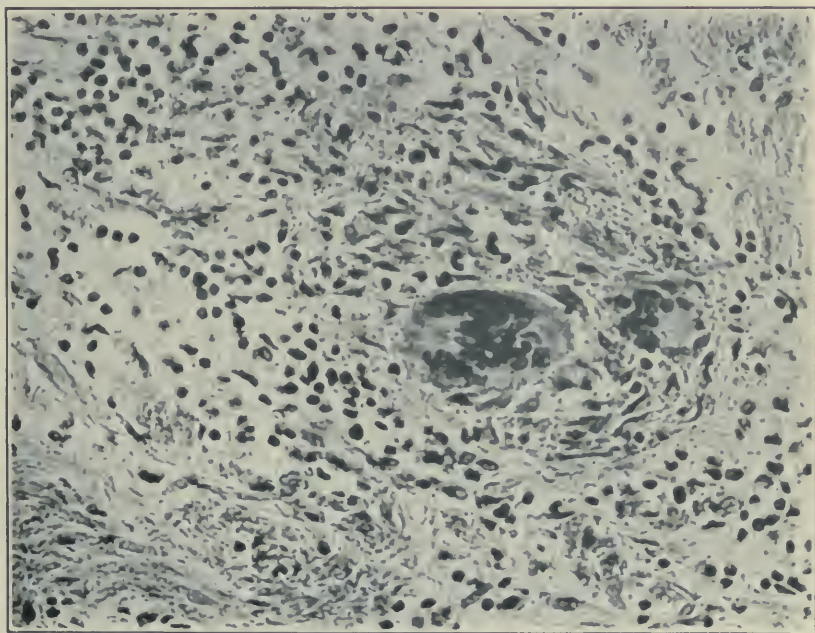


Fig. 7.—High-power view of miliary gumma shown in Fig. 6. Plasma-cells, giant-cells, fibroblastic and angioblastic proliferation.





veals itself in the subepithelial infiltrations of plasma cells and lymphocytes, and in the hyperplasia of the primitive lymph nodes. I have examined the prostates of only a few cases of old syphilis for spirochetes, and the few attempts were unsuccessful. As far as the histologic picture of latent syphilis of the prostate is concerned it is certainly less easily recognized in this organ than in others, but this may be due to its being covered up or complicated with changes due to chronic prostatitis of other etiology. Gumma of the prostate must be extremely rare as compared with that of other organs, else it would have been recognized by this time. It is therefore, possible that the prostate may possess a relatively higher immunity to spirochete localization and growth than other organs, and that the lesions heal sooner than in other tissues. It remains for future investigation to decide this question.

This first positively demonstrated case of syphilis of the prostate shows that the prostate may present characteristic lesions of syphilis relatively early in the course of the infection, and that these may exist in a marked degree without causing any enlargement of the organ, or any symptoms directly referable to it. The histologic picture of syphilis in this organ is identical with that found in the myocardium, aortic wall, adrenals, and other organs.

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FLOCCULATION REACTIONS IN SYPHILIS. WITH  
ESPECIAL REFERENCE TO THE MEINICKE  
AND SACHS-GEORGI REACTIONS

BY SAMUEL A. LEVINSON, M.S., M.D., CHICAGO, ILL.

*From the Department of Pathology and Bacteriology and the Laboratory of  
Physiological Chemistry, University of Illinois, College of Medicine*

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EVER since Landsteiner, Müller, and Poetzel<sup>1</sup> found that alcoholic extracts of nonsyphilitic organs could be used in the Wassermann reaction and thereby discredited the specific antibody conception of the mechanism, efforts have been made either to modify the original technic, or to supplant it with a simpler reaction. Sachs and Rondoni,<sup>2</sup> Noguchi<sup>3</sup>, and others sought to prepare various artificial antigens; of these however, only the cholesterinized antigen has come into general use.

Other workers sought to standardize the technic. Kolmer<sup>4</sup> and his collaborators have demonstrated the large number of factors capable of producing divergent results. The German Health authorities are preparing an antigen issued by a central laboratory, hoping thus to secure greater uniformity in the test. However, when one takes into consideration the number of other biologic reagents necessary, such as red cells,amboceptor, and complement, one can readily see that uniformity of the antigen alone will not necessarily solve the problem.

Since the technic employed by different individuals often gives discordant results, because of the exact titrations necessary, a simplified technic for the serodiagnosis of syphilis would appear to be in order. The difficulty in the preparation of the antigen and the cumbersome technic in general warrants the search for a simpler reaction for syphilis.

The question of specificity and standardization of the Wassermann reaction is not within the range of our present discussion. To avoid the uncertainty of the complement-fixation reaction many investigators have tried other methods. Jakobaus<sup>5</sup>, Streng and Karvonen<sup>6</sup>

have introduced the conglutination reaction, but their results were not as satisfactory as those obtained with the Wassermann reaction.

Efforts made to find other serum reactions to replace the Wassermann technic have resulted most often in methods of a precipitation either of the antigen by the serum, or of some serum component by a biologic or chemical reagent.

We will mention here very briefly some attempts to design simpler methods for the serodiagnosis of syphilis.

#### SERUM REACTIONS IN SYPHILIS OTHER THAN THE WASSERMANN REACTION

*Hirschfeld-Klinger Coagulation Reaction*<sup>7</sup>.—When tissue extract, such as beef heart, is digested with syphilitic serum it loses its ability to coagulate blood. The effect depends on adsorption of lipoids of tissue extract by serum constituents and is fundamentally similar to the Wassermann reaction. The Hirschfeld-Klinger reaction because of its large number of nonspecific reactions, did not replace the Wassermann reaction as it was originally intended to do.

*Fornet and Schereschewsky*<sup>8</sup> have shown that serums from tabetics and paralytics give a precipitate with serums from positiveluetics. Part of the serum used is undiluted, and is poured over the remainder which is diluted 5 to 10 times, and this mixture is placed in small test tubes. First the specific heavier mixture mixes with the lesser strongly diluted mixture, and then by slanting the tubes, the lighter specific fluid comes to the surface. For controls, definite syphilitic and nonsyphilitic serums are used. The tubes are placed at room temperature for two hours. The positive tubes show at the junction of the two fluids, a fine ring which is absent in the definite nonluetice sera.

*Klausner's Serum Reaction*.—When 0.6 c.c. distilled water is added to 0.2 c.c. of fresh, active, absolutely clear serum, a distinct flocculant precipitate separates out in from 7 to 15 hours and this property is more marked in syphilitic sera than in normal sera. While this reaction is not specific for syphilis, it is almost invariably present in certain stages of syphilis. This property is not due to excess of globulin present in syphilitic sera according to the later studies of Klausner, but probably to the high lipid content of syphilitic serum.

Sachs<sup>10</sup> has shown that the serum globulins are less stable and more easily precipitated in syphilitic serums as well as in other infectious diseases due to changes in acidity. When serum is inactivated the



precipitate is increased to a certain extent because of an alteration in the OH and H ion balance. But Klausner's reaction can only be used in active serums. Sachs and Nathan have shown that on inactivating the serum with distilled water an ultramicroscopic precipitate is brought about when any pure chemical as normal HCl is added to it. This, however, did not bring practical results.

*Porges-Meier Reaction*<sup>11</sup> is based upon the fact that syphilitic serums produce flocculi in solutions of lecithin and similar salts. An equal amount of inactivated, clear patient's serum is mixed with 1 per cent sodium glycocholate in distilled water. This mixture (together with known normal and luetic controls) is kept at room temperature for from 18 to 24 hours. Positive reactions give distinct coarse flocculi; a turbidity or a faint precipitate is considered negative.

In this connection it may be mentioned that investigators such as Müller and Landsteiner<sup>12</sup>, Elias, Neubauer, Porges and Salomon<sup>13</sup>, Hermann and Perutz<sup>14</sup>, Sachs and Altmann<sup>15</sup>, Bruck and Hidaka<sup>16</sup>, Teruuchi and Toyada<sup>17</sup>, Levaditi and Yamanouchy<sup>18</sup>, Fleischmann<sup>19</sup>, Hecht<sup>20</sup>, Hesberg<sup>21</sup>, Munk<sup>22</sup>, and others, have used lecithin, salts of bile acids, alkalies, sodium oleate, cholesterin, vaseline, courin, palmatin, stearin, sodium salts, potato extracts, shellac emulsions and numerous other combinations without definite results.

*Jacobsthal*<sup>23</sup> has shown that by adding luetic serum to organ extract as in the Wassermann reaction, a precipitate is observed which can be demonstrated by means of a dark field. Bruck and Hidaka<sup>16</sup> could obtain the same results macroscopically.

*Hermann-Perutz Reaction*<sup>24</sup> consists of a precipitation resulting from the interaction of clear inactive serums with a solution of sodium glycocholate, alcohol, and cholesterol in distilled water. The test is as follows: Solution 1 (stock solution diluted 1:20 with distilled water before use) consists of sodium glycocholate 2 gms., cholesterol 0.4 gms., 95 per cent alcohol 100 c.c.; solution 2 is a 2 per cent solution of sodium glycocholate in distilled water. Add 0.4 c.c. of clear inactive serum (heated at 56° C. for one half hour) in a small test tube to 0.2 c.c. of solution 1 and 0.2 c.c. of solution 2. The tubes are plugged with cotton and set aside at room temperature for 24 hours, after which the presence or absence of precipitation is noted. Known normal and luetic serums in distilled water are used as controls.

None of the above reactions has been found absolutely specific, and none has been generally adopted; the far greater accuracy of the

Wassermann reaction having made it the method of choice. Normal serum also precipitates lipoids, with this distinction, that in normal serum the zone of precipitation is smaller and longer delayed than in syphilitic serums.

*The Bruck Test*<sup>25</sup> is a serochemical reaction for syphilis. 0.5 c.c. patient's serum is mixed with 2 c.c. distilled water and allowed to remain at room temperature for 10 minutes and 0.3 c.c. of a 25 per cent solution of  $\text{HNO}_3$  is added. The tube is shaken and again allowed to remain at room temperature for 10 minutes and 16 c.c. distilled water added to the contents. The tube is again allowed to remain at room temperature for 10 minutes, and is shaken several times for 30 minutes and allowed to remain at room temperature for 12 hours. When the solution is cloudy or presents opaqueness, the result is considered positive; but when the solution is transparent or presents but a little cloudiness the result is negative. This reaction does not compare favorably with the Wassermann reaction and is negative in a large number of clinically positive cases of syphilis.

*Vernes Phenomenon*<sup>26</sup>. In the Wassermann test a positive reaction is characterized by the absence of hemolysis, and a negative reaction by complete hemolysis. There are several degrees of color changes, the interpretation of which depends on the individual worker and is expressed by plus signs. Vernes devised a colorimetric scale consisting of 8 tints numbered from 0 to 8, zero representing the absence of hemolysis, and 8 the maximum hemolysis or deepest shade of red. By charting these results graphically Vernes at first believed that the curves obtained with syphilitic serums possessed certain fundamental characteristics, but other investigators showed they were not always able to differentiate normal from syphilitic serums by colorimetric readings, because under certain conditions the two gave the same results. These color changes were charted on a given scale and it was noted that syphilitic serums occupied a given part of the syphilitic chart or "graphique" as compared with normal serums.

Vernes began his experiment as follows: A series of approximately 40 tubes, each containing 2 c.c. of a colloidal suspension of ferric hydrate, 0.2 c.c. human serum and 0.9 per cent  $\text{NaCl}$ , were placed in an incubator at  $37^\circ\text{C}$ . for 40 minutes. Flocculation occurred in certain tubes, disappeared either abruptly or progressively in other tubes and reappeared in a later series of tubes, constituting periodic zones of flocculations. If other mineral substances in colloidal states were

substituted for ferric hydrate the periodic rhythmicity of flocculation was changed but variation between normal and syphilitic serums occurred constantly. In order then to produce flocculation with syphilitic serums and not with normal serums, an organic colloidal preparation was necessary, not a mineral suspension. An extract of horse heart diluted with distilled water was used to make the proper colloidal suspension. 0.4 per cent NaCl was used for the electrolyte. The complete reaction is a two-stage reaction as follows: Stage I: 0.2 c.c. of human serum which has been inactivated at 55°C. for 20 minutes, 0.8 c.c. horse heart extract diluted 1:40 in 0.9 per cent NaCl, and 0.8 c.c. pig serum. Tubes are placed in incubator at 37°C. for one hour and 25 minutes. Stage II: 0.8 c.c. sheep cells (titrated and made up in 50 per cent hypertonic saline solution) is added to each tube and again incubated for one half hour and centrifuged. In the first stage no flocculation results with normal or syphilitic serums because pig serum prevents flocculation by virtue of its anti-flocculent power. After centrifugalization (as in the second stage) normal and hemolytic serums may be entirely free from a hemoglobin tinge but there may be intermediate degrees of color tints between deep red and colorless which constitute a syphilitic index which may be of some importance in the control of treatment.

*Meinicke Reaction.*<sup>27</sup> This test is based on the hypothesis that the reaction between serum and extract takes place when extract colloids disturb the isotonicity of salt solution permitting the union of seroglobulins and lipid extract. This reaction is greatly intensified in the positive syphilitic serums as compared with negative. The various forms of Meinicke's reactions are (1) Water method; (2) Salt solution method; (3) Third Modification.

(1) *Water method.* Wassermann antigen diluted with distilled water flocculates all negative serums, while the positive serums show a characteristic opalescent turbidity. Positive serum does not flocculate as the globulin cannot be released in distilled water medium, but the lipoglobulin complex through the action of the lipoids compensates itself by keeping the globulins in distilled water solution. This method possessed many faults as weak flocculation would often result in strongly positive Wassermann serums, and heavy flocculations in negative Wassermann serums. Meinicke then devised the following method:

(2) *Salt Solution Method.* This method, intended to overcome the



difficulties of the previous method, consists of a two-phase reaction. Extract of syphilitic liver diluted with distilled water will flocculate both normal and syphilitic serums. The addition of salt solution in varying concentrations to both serums would dissolve the precipitate in the negative and not in the positive; in fact, the precipitate in the positive tubes becomes intensified. (See references 28 for those who investigated the Meinicke reaction).

For the reason that spinal fluid contains albumins, it will not flocculate with the first or second Meinicke methods, but flocculation will occur, however, in what is termed the Third Modification and also in the Sachs-Georgi reaction.

(3) *Third Modification.* Using an antigen prepared according to the method of Wassermann and with the addition of horse heart extract, he was able to get flocculation in the strongly positive serums. This is a one-phase reaction consisting of covering the contents of the tube with approximately a 2 per cent solution of NaCl. In many cases this modification gave a positive reaction earlier than the Wassermann reaction. In spinal fluids, however, the Third Modification will show flocculation and certain concentrations of NaCl will flocculate negative Wassermann serums. This phase of the question requires more study as Meinicke reports a difference of 5 to 10 per cent between Wassermann reaction, Meinicke (Phase I and II) reaction, and Third Modification. The reasons for these differences are not given by him.

The explanation of this reaction is as follows: The tissues of an organism immunized against a certain substance has the power to combine with an antigen faster and more intensely than through an organism which has not been so immunized. This specific reaction not only occurs with tissue cells but may also take place with blood serum. The various forms of immunity reactions are simply expressions of the numerous agents which react in various combinations in a progressively increasing manner so that it is possible that these various agents can combine with one another. This hypothesis then is based on the study of precipitation, agglutination, anaphylaxis, hemolysis, and bacteriolysis. By inactivating the serum the strength of the reaction is changed in two ways, namely, the seroglobulin molecule is heavier than the salt solution molecule, and conversely, the heavier the concentration of the solution the greater is the combining power with the albumin molecule in the inactive

serum over that in the active serum. The fundamental principle involving these two investigations is based upon the great binding power of the salt with the heated serums.

The water and salt solution methods are used as controls for the Third Modification of the Meinicke reaction. The results of this reaction compare favorably with the Wassermann reaction.

*Sachs-Georgi Reaction.*<sup>29</sup> This is a physico-chemical reaction between seroglobulins and lipid extract. It has been shown that the globulins in syphilitic serums are increased in amount and that the flocculate which occurs in this reaction is a lipoglobulin aggregate. The modified technic of this reaction is as follows: Three drops of inactive serum or 6 drops of spinal fluid plus 1 c.c. of an 0.85 per cent NaCl plus 0.5 c.c. cholesterinized beef or human heart extract (cholesterinized beef heart extract will flocculate syphilitic serum only) which has been previously diluted 1:6 with 0.85 per cent NaCl is put in an incubator at 37° C. for from 18 to 24 hours. A reading is taken and positive tubes show a flocculation. Serum mixed with alcohol is used as a control for this reaction. The tubes are allowed to remain at room temperature overnight when a second reading is taken. Positive tubes show a flocculation, negative tubes remain clear. For reading the results of this reaction as well as for the Meinicke reaction, an agglutinoscope, a dissecting microscope with a number 8 or 9 lens, an ocular from a microscope, or an ordinary magnifying lens may be used.

The Sachs-Georgi reaction is the simplest of all the flocculation reactions. The preparation of the antigen and the technic of the test is so simple that the clinician can compare his data with the serologic results; and also the serologist may use this simple reaction as a check for the Wassermann reaction.

#### EXPERIMENTAL INVESTIGATION OF WASSERMANN, MEINICKE, AND SACHS-GEORGI REACTIONS WITH ANIMAL SERUMS

A comparison was made between the Wassermann, Meinicke, and Sachs-Georgi reactions using animal serums. It is known that the serums of certain animals will give a positive Wassermann reaction. Friedmann<sup>30</sup> has shown that by using inactivated beef, goat, dog, and rabbit serums one can easily obtain a positive Wassermann reaction. Inactivated cow, guinea pig, and goose serums did not give

a positive Wassermann reaction. This investigator has shown that in flocculation reactions, precipitation with lecithin, sodium glycocholate and distilled water may result with normal animal serums. Manwaring<sup>31</sup> examined active animal serums and was able to demonstrate a positive Wassermann reaction with beef, horse, and goat serums. The following tables show the relationship between the Wassermann, Meinicke, and Sachs-Georgi reactions using both active and inactive animal serums.

TABLE I  
NORMAL ANIMAL SERUMS\*

ANIMAL	WASSERMANN		SACHS-GEORGI		MEINICKE			
	ACT.†	INAC.†	ACT.	INAC.	PHASE I		PHASE II	
					ACT.	INAC.	ACT.	INAC.
Chicken	+	±	+	+	+	+	+	+
Duck	±	0	0	0	±	±	±	±
Cat	+	+	0	+	+	±	0	±
Horse	+	+	+	+	+	+	+	±
Beef	+	±	+	0	+	+	±	±
Steer	+	+	+	+	+	+	+	±
Goat	+	+	+	+	+	+	+	+
Pig	+	+	0	+	+	+	0	±
Rabbit	± — +	+	0	0	+	±	+	±

\*Modified from Paul Konitzer, *Ztschr. f. Immunitäts. u. Exper. Therap. Orig.*, 1920, # 30.  
†Act. = Active; Inac. = Inactive Serum.

TABLE II  
PRECIPITATING RABBIT SERUMS\*

ANIMAL	WASSERMANN		SACHS-GEORGI		MEINICKE			
	ACT.†	INAC.†	ACT.	INAC.	PHASE I		PHASE II	
					ACT.	INAC.	ACT.	INAC.
Chicken	+	+	0	0	+	+	+	+
Duck	+	+	±	0	+	+	+	+
Cat	+	+	0	±	+	+	±	+
Horse	+	+	±	0	+	+	+	+
Beef	+	+	±	0	+	+	+	±
Steer	+	+	±	+	+	+	±	+
Goat	0	+	+	0	+	+	+	0
Pig	+	+	±	0	+	+	0	+
Deer	+	+	0	0	+	+	+	+
Goose	+	+	0	+	+	+	+	+

\*Modified from Paul Konitzer, *Ztschr. f. Immunitäts. u. Exper. Therap. Orig.*, 1920, # 30.  
†Act. = Active; Inac. = Inactive Serum.

The above tables show that the Sachs-Georgi reaction and Meinicke reaction also give a positive flocculation reaction with certain animal serums; however, there exists no parallelism with the Was-



sermann reaction. There seems to be no definite advantage in using inactive serum. With certain serums flocculation seems to increase, with others it is less.

#### RELATION OF ABOVE REACTIONS TO THE CLINICAL DIAGNOSIS OF SYPHILIS

Most of the above tests were designed to supplant the Wassermann reaction, but it may readily be seen that not only are some of these reactions as complicated as the Wassermann reaction but they have also been proved inferior when the clinical diagnosis is considered, and certainly cannot be used to supplant the Wassermann reaction. Not only were some of the above mentioned flocculation reactions negative when the Wassermann reaction was positive, but they were negative also in definite clinical cases of syphilis with strongly positive Wassermann reactions.

Comparing the serologic data obtained of these reactions with the clinical studies of the cases, we find the Meinicke and Sachs-Georgi reactions most trustworthy. And because of the marked simplicity of the Sachs-Georgi reaction as compared with the Meinicke reaction we have made a more detailed study of this test, and have compared it with the Wassermann reaction and clinical symptoms both of syphilitics and nonsyphilitics.

The results of our previous investigations<sup>32</sup> show that in an examination of over 1000 cases with both the Wassermann and Sachs-Georgi tests, there was an agreement in 92 per cent. This percentage is in accord with the results of other investigators as Table III shows. Table IV gives a detailed comparison of the Sachs-Georgi and Wassermann reactions; also showing our results as compared with those of other investigators. In spinal fluid examination in cases of neurosyphilis,<sup>33</sup> there was an agreement between Wassermann and Sachs-Georgi tests in 79 per cent. As our records show, the Sachs-Georgi reaction was positive in a larger number of clinically positive cases of syphilis than the Wassermann reaction, so that although the percentage of agreement between these two reactions may not be high, nevertheless, when the Sachs-Georgi reaction is compared with the clinical diagnosis of syphilis the percentage increase becomes higher. The response of the positive cases to antisyphilitic treatment as determined by the Sachs-Georgi reaction is also corroborative of its marked efficiency.

TABLE III

PERCENTAGE AGREEMENT BETWEEN WASSERMANN AND SACHS-GEORGI REACTIONS

INVESTIGATOR	PER CENT	INVESTIGATOR	PER CENT
Sachs-Georgi <sup>29</sup>	94.94	Konitzer <sup>38</sup>	86.
Löns <sup>34</sup>	95.5	Schroder <sup>39</sup>	85.2
Sheer <sup>35</sup>	94.38	Weichard and Schroder <sup>40</sup>	82.
Gaethgens <sup>36</sup>	93.7	Hauck <sup>41</sup>	80.66
Meyer, Lipp, Nathan, Munster <sup>37</sup>	93.	Levinson and Petersen <sup>33</sup>	78.5
Levinson and Petersen <sup>32</sup>	92.	(Neurosyphilis)	

The Sachs-Georgi reaction because it is simple and practical enables the clinician to better understand serologic tests and their relation to the clinical findings. It can be elicited earlier and remains positive later than the Wassermann reaction; it is not influenced by treatment to the extent of becoming negative after one or two injections of salvarsan; it is present in congenital cases of syphilis as well as in latent syphilis; and in cases of neurosyphilis.

Since there has not as yet been a sufficiently large number of cases reported by investigators to permit a trustworthy comparison, we are of the opinion that for the time being the Sachs-Georgi reaction should not supplant the Wassermann reaction, but may supplement it. For this reason, the various factors entering into this reaction will be analyzed, and an attempt made to explain the mechanism of the flocculation.

## MATERIAL FOR SACHS-GEORGI REACTION

A detailed study of the material used and the technic employed in the Sachs-Georgi reaction will be made, especially in reference to the advisability of employing these various factors.

*Inactivation of serum and its relation to the reaction.* It is known that the complement varies in different specimens of serum, and for this reason Wassermann, Bauer,<sup>52</sup> and others heat the serum to 55° C. for one half hour to destroy the native complement. They substitute for this unknown factor in the Wassermann system a uniform amount of guinea pig complement of known activity. In the system of Hecht<sup>53</sup> and Tschernogubow<sup>54</sup> the serum is not heated, thus utilizing the native complement in the serum and making the reaction more sensitive. A study of the effect of active or inactive serums on the Wassermann reaction was undertaken by Noguchi,<sup>55</sup> who came to the following conclusions: "In the majority of active

human serums irrespective of sources there exists a constituent which fixes complement when mixed with certain proteins such as, nucleoproteins, peptone, albuminoses and many other autolytic decomposition products of proteins. This is known as the proteotropic fixation group in contradistinction to the lipotropic fixation due to the action of certain lipoids upon syphilitic serum. This proteotropic group is destroyed by heating to 55° C. for 20 minutes, while the lipotropic fixation is not abolished. It becomes evident, then, that when one employs as an antigen an alcoholic or aqueous extract of macerated organs inactivated serum must be used, because the antigen preparations contain various proteids and are liable to give a nonspecific proteotropic fixation with active serum."

TABLE IV

COMPARISON OF WASSERMANN REACTION AND SACHS-GEORGI REACTION SHOWING OUR RESULTS AS COMPARED WITH THOSE OF OTHER INVESTIGATORS

REACTION	RESULTS						TOTAL		
Wassermann		+			±		0		
Sachs-Georgi		+			±		0		
Sachs-Georgi <sup>29</sup>	614	32	20	23	—	—	37	23	2016
Georgi <sup>42</sup>	331	19	32	20	—	2	32	7	1228
Nathan <sup>43</sup>	598	—	55	—	—	—	96	—	866
Nathan-Weichbrodt <sup>44</sup>	39	—	—	—	—	5	7	—	141
Weichardt-Schroder <sup>40</sup>	31	—	2	—	—	—	2	—	2
Reich <sup>28</sup>	49	5	—	—	7	9	2	9	126
Lesser <sup>28</sup>	162	—	57	—	—	—	116	—	1165
Meyer <sup>37</sup>	148	13	10	—	12	11	1	1	404
Konitzer <sup>38</sup>	175	—	31	—	—	—	44	—	438
Munster <sup>37</sup>	116	1	2	4	—	—	7	1	23
Löns <sup>34</sup>	183	—	8	4	—	—	3	5	337
Zurhelle <sup>45</sup>	663	—	133	—	—	—	71	—	1167
Scheer <sup>35</sup>	129	1	4	—	28	—	17	—	199
Zimmern <sup>46</sup>	193	57	16	7	21	31	6	22	501
Gathgens <sup>36</sup>	110	1	11	13	2	9	23	1	530
Frankel <sup>47</sup>	83	—	6	—	3	—	6	—	179
Raabe <sup>48</sup>	569	—	5	—	—	47	8	37	1005
Wolffenstein <sup>49</sup>	264	—	15	—	—	—	134	—	578
Frommherz <sup>50</sup>	48	1	2	3	24	17	2	4	197
Baumgartels <sup>51</sup>	1303	152	105	75	129	194	72	111	4839
Levinson-Petersen <sup>52</sup>	199	11	6	3	—	3	51	11	755

In the Sachs-Georgi reaction the best results are obtained by inactivating the serum at 55° C. for 20 minutes. Mandelbaum<sup>56</sup> has carried out experiments along this line in which positive serums were



inactivated at various degrees ranging between 45° C. to 65° C. Above 55° C. the number of positive cases became less in number. It is best to inactivate the serum undiluted. Hauck<sup>57</sup> states that cold temperatures influence the flocculation in some way and that more nonspecific reactions occur at lower temperatures than higher temperatures. The best results obtained which are characteristic for flocculation as well as for the Wassermann reaction is when the serum is heated at 55° C. for one-half hour.

*Diluting solution.* Neukirch<sup>58</sup> has shown that a larger number of nonspecific reactions occur in undiluted serums than in diluted serums. For the Wassermann reaction physiologic salt solution can be used as a diluting agent, but in the Sachs-Georgi reaction, an 0.85 per cent NaCl must be used. This salt is equimolecular and has an isoelectrical point for the seroglobulins and is the optimum concentration needed to produce flocculation. Neukirch<sup>58</sup> has also tried other salts as sodium nitrate, sodium sulphate, sodium acetate, sodium bromide, potassium chlorate, and magnesium chloride, but these salts which were used in varying concentrations did not prove as satisfactory as an 0.85 per cent NaCl solution. The diluting agent must not be added to the antigen too rapidly or too slowly. In the diluting of the serum this factor plays no appreciable rôle.

*Antigen.* The most important factor in the standardization of the Wassermann reaction as well as for the specificity of the Sachs-Georgi reaction is the antigen. Although artificial antigens such as, lecithin, salts of bile acids and soaps have been used with some degree of specificity in syphilitic serums, it is entirely a matter of choice, as the ultimate usefulness of an antigen is dependent on the care with which the extract was standardized.

The preparation of the proper antigen is perhaps the fundamental factor in the success or nonsuccess of the Sachs-Georgi reaction. Extracts of various organs can be used but the most satisfactory results have been obtained with extracts prepared from human and beef heart. An alcoholic solution of cholesterol is added to the extract, the exact amount, however, being determined by titrating the antigen against negative and positive serums using varying amounts of cholesterol. This method of titration has been described in a previous article.<sup>32</sup>

When the extract is properly made it is quite clear, but before use

when the antigen is diluted 1:6 with salt solution it is faintly opalescent and does not flocculate after standing several days. For the Wassermann reaction this antigen can be used in dilution of 1:10.

Several antigens which we prepared 8 months ago, and which have been standing at room temperature, were tested recently in the Sachs-Georgi reaction and the Wassermann reaction and found as active as when first prepared.

*Incubation.* The specificity of the flocculation reaction also is dependent upon the period of incubation. In the original technic of Sachs-Georgi the tubes were incubated for 2 hours and read, then allowed to remain at room temperature for 24 hours before the final reading. A large number of nonspecific reactions resulted especially in cases of tuberculosis, tumors, and typhus. Steiling,<sup>59</sup> Gaethgens,<sup>56</sup> Schoenfeld<sup>60</sup> and others have shown that by incubating the tubes at 37° C. for from 18 to 24 hours and a first reading taken, and then allowing the tubes to remain at room temperature overnight, these nonspecific reactions could be obviated. By this procedure the agreement between the Wassermann reaction and the Sachs-Georgi reaction reached a higher percentage. Sachs and Georgi have also adopted the latter incubation time.

*Reading of Results.* The positive cases present a flocculation which either may be finely granular, having a snow storm appearance, or which may be finally precipitated as a coarsely granular mass at the bottom of the tube. The very definite cases may be precipitated at the end of 2 hours' incubation; however, by allowing the tubes to remain at room temperature overnight all positive cases may show the same results. The negative cases may remain perfectly clear, or a very slight precipitate may collect at the bottom of the tube which can readily be differentiated from positive findings. By experience one may grade the degree of the reaction on a 1 to 4-plus basis.

As a rule most of the readings can be made with the naked eye. The earlier investigators of the Sachs-Georgi reaction, as well as of the Meinicke reaction, used the agglutinoscope devised by Kuhn and Voit. A good magnifying lens from a dissecting microscope, or an ordinary ocular may be used with satisfactory results if the tubes are held against a black background.

Meyer<sup>61</sup> and Gaethgens<sup>56</sup> have found it advisable to centrifuge the tubes for 20 minutes at low speed after incubation thus saving time.

Also by concentrating the precipitate one is able to eliminate non-specific reactions. In doubtful cases we have centrifuged the tubes at low speed for 20 minutes and by pouring off one-half the supernatant liquid we were able to concentrate the flocculation into one-half the amount of fluid, thus making the reaction doubly certain.

#### MECHANISM OF FLOCCULATION REACTIONS

The mechanism of the Wassermann reaction is based upon the disappearance of complement in the mixture of antigen and antibody and is called "complement fixation;" if the complement has been deviated by the combination of antigen and antibody thus preventing participation in the hemolytic process, it is called "complement deviation." However, the question of hemolysis does not enter into the mechanism of the Sachs-Georgi reaction as only one biologic reagent (antigen) is used, instead of 4 (antigen, red blood cells, amboceptor, complement) in the Wassermann system.

The numerous investigations into the phenomena of complement-fixation reaction resulted in the presentation of 2 theories: One being the specific antibody-antigen reaction in connection with Ehrlich's side chain theory; the other the Bordet adsorption theory based upon a physical or a physicochemical concept. With further advances into the study of the chemistry of colloids a large number of investigators came to the conclusion that the Bordet-Gengou phenomenon is simply a precipitation of colloids.

At first Zangger as well as Landsteiner,<sup>62</sup> studying the Bordet adsorption theory, came to the conclusion that the reaction between the immune bodies and antigens is in its entirety a growth of colloidal particles, and as to specific complement fixation, Moreschi<sup>63</sup> concludes that it is a precipitation of antigen by antibody. Gay<sup>64</sup> and others have shown that the adsorption of the complement is a phase of the reaction similar to the aggregation of ultramicroscopic colloidal particles.

The mechanism underlying the reaction discovered by Bordet and Gengou remained in doubt for a long time until Moreschi<sup>63</sup> demonstrated the complement-binding reaction between the antialbumin group and its accompanying antigens.

We cannot enter here into a detailed discussion of the explanation of the mechanism of the Wassermann reaction, but it is the con-



sensus of opinion among investigators that this reaction is a physical or a physicochemical reaction. Wassermann<sup>70</sup> has recently revised his old conception of the mechanism of his reaction as being an antigen-antibody reaction, for he has shown that when this reaction was first formulated, antigens as normal lipoids, such as lecithin, or alcoholic extracts of normal organs were not used. It was not known, in the early stages of this reaction, that the amboceptor may be lipotropic. Wassermann thoroughly investigated this subject and was able to demonstrate that syphilitic serum contains a substance which he calls "Wassermann substance." This substance is capable of combining with lipoids forming a new aggregate which he calls "Wassermann aggregate." These Wassermann aggregates are evenly composed and can easily go back into solution, as the two specific components (amboceptor and lipoid) are held together in a loose combination. Under favorable conditions these two elements may enter into a combination again. There is a reversible binding power between the Wassermann substance and the added antigen in which the complement is bound together very strongly. This newly isolated substance has all the characteristics of an amboceptor. According to the definition, the Wassermann substance undoubtedly belongs to the class of antibodies, but primarily it is certainly an antibody for human lipoids, and probably later this substance may be isolated from animal cells.

It was very interesting from this standpoint to note the relationship the various serum reactions for syphilis, especially the flocculation reactions, have with the Wassermann reaction. Wassermann studied the Sachs-Georgi reaction to determine if this reaction showed a qualitative relationship to the Wassermann reaction. The precipitate from the Sachs-Georgi reaction was washed, dissolved in salt solution and tested to show the relationship the isolated partial antigen has to the Wassermann substance. When the latter is added to the partial antigen solution a positive reaction is the result, and conversely, when the partial antigen from the Sachs-Georgi reaction is added to the Wassermann system, a positive reaction also takes place. *This is conclusive evidence that the Sachs-Georgi reaction is qualitatively similar to the Wassermann reaction, and that the foundation for all serodiagnostic methods for syphilis is the formation of the Wassermann aggregates.*

It becomes evident then, that the newer flocculation reactions, such as the Meinicke and Sachs-Georgi reactions might throw some light on the colloidal changes of the seroglobulins characteristic for syphilitic serum, without attempting to explain complement binding action. Certain antibodies are called upon to unite with the complement (Wassermann reaction), but the conditions of the serum such as disturb the electrochemical affinity and dispersion, may be so altered, as to bring about a rearrangement of the serum globulins which enables them to unite with the lipoidal extract to form a colloidal precipitate. In the Wassermann and flocculation reactions definite colloidal aggregates result, and for syphilis there appears to be a special affinity between the serum globulins and lipoidal extract resulting in the formation of colloidal aggregates. According to Sachs the difference between the Wassermann reaction and the flocculation reactions is that in the former there is no definite macroscopic precipitate at the beginning, but instead there is a growth of the globulin particles which continues until gross precipitation takes place.

Acids increase and alkalis decrease the speed of these reactions. (Nathan<sup>65</sup> added acids, inulin, and bacterial suspensions to negative Wassermann serums and was able to obtain a positive Wassermann reaction; the Sachs-Georgi reaction became positive later on. The flocculations which occurred with the Sachs-Georgi reaction were not characteristic for syphilis, since the seroglobulins were affected in some way.) In the Meinicke reaction, when normal HCl of 1:500 dilution was used, some tubes showed flocculation, others not; but in the Sachs-Georgi reaction there is a scant flocculation when this chemical is added which can easily be differentiated from positive flocculations.

Herzfeld and Klinger,<sup>28</sup> Saligmann,<sup>66</sup> Much,<sup>67</sup> Elias, Porges, Neubauer and Solomon<sup>13</sup> investigated the Wassermann and flocculation reactions with various reagents and came to the conclusion that no actual difference exists between the two. Hecht,<sup>53</sup> Meinicke,<sup>27</sup> and others have shown that the union of extracts and antigen resulted in an anticomplementary precipitate. Michaelis and Davidsohn<sup>68</sup> are of the opinion that with immunity reactions, especially the Wassermann reaction, the affinity between antigen and antibody cannot be explained on the basis of adsorption.

Meiniecke explains the flocculation phenomenon resulting from the union of luetic globulins with extract by saying, "that the combination of these 2 elements takes place in a salt solution medium. In positive serum the reaction is intensified and there is adsorption of salt from solution, while with the negative serum there is a weak adsorption of NaCl. The positive serums contain, therefore, flocculi which have a strong affinity for NaCl, the negative serums having a weak affinity for NaCl."

According to Sachs and Georgi flocculations result from the union of extract and seroglobulins which are characteristic for lues, and these two elements have a definite affinity for each other.

There are two possible factors which enter into the mechanism of flocculation reactions: (1) The OH ion is increased when luetic serum is heated to 55° C.; (2) Michaelis<sup>69</sup> has also shown that heat changes the isoelectrical point of the serum and that when the globulins are changed through inactivating the serum, the isoelectrical point is disturbed and the H ion concentration is lessened; thus normal inactive serum can be made to flocculate upon the addition of HCl. Sachs, Schmidt, and Hecht have demonstrated that a rearrangement of the isoelectrical point of the seroglobulins in luetic serum is the result of the formation of acid albuminate bodies. Flocculation in normal and luetic serums do not take place suddenly but gradually.

Alcohol and NaCl used in diluting the extract have no effect upon the globulins, or upon the inactivated serum mixed with diluted extract. Solutions of alcohol and NaCl in higher concentration may produce precipitation but alone and in such high concentration they are not used in flocculation reactions.

Meiniecke is of the opinion that in the first phase of his reaction the precipitating power of extract and distilled water is brought about through a diminution of its binding power with the globulins. (This is not characteristic for precipitation in luetic serum and certainly is not true in a medium of high salt concentration, but that NaCl, under ordinary circumstances adsorbs water from the precipitated globulins. Bechhold investigating this subject says, "that globulin flocculi under certain conditions is bound with water as a result of its weight.") Also Meiniecke's water method in which



flocculation takes place in certain zones in negative serum which has been diluted with water, is in accord with the above explanation.

Spinal fluid does not flocculate in the first phase of the Meinicke reaction, and it is explained that because of the relatively high water content of the spinal fluid, the water diluted extract will not flocculate the spinal fluid upon the removal of NaCl from solution, while the Sachs-Georgi reaction and Third Meinicke reaction will flocculate spinal fluid.

The above explanations would seem to indicate that flocculation comes to a stand still when the individual colloidal globulin particles adsorb water, and that these particles through adsorptive powers become larger complex units. In order to determine whether the extract lipoids play a rôle in flocculation, Meinicke used Sudan IV to stain the extract particles. The stain is not thrown down when organ extract and luetic serum is mixed. Sudan IV stains the lipoglobulin aggregate, but this condition does not explain the reason that lipoids do not combine with NaCl. Meinicke came to the conclusion then, that since Sudan IV stains extract lipoids only, the latter do not enter into the process of flocculation. Hecht<sup>53</sup> having the opposite opinion, that from his studies of the complement with flocculations resulting in positive serums, IX gave nothing else than an antigen complex characteristic for precipitation in luetic serum.

Joel<sup>28</sup> used Osmic acid to stain the extract lipoids and reached the same conclusion Meinicke did. The black staining particles were mixed with luetic serum, and the flocculations centrifuged; by this means the black staining flocculations can be recognized. Joel, drawing his conclusion from Meinicke, says, "that the precipitation of lipoidal extracts is not characteristic for the Meinicke reaction, although one cannot say very definitely that there are no extract lipoids in the precipitation. But that in the course of the reaction there is set up a new individual chemical process of an entirely different nature."

In a dark-field examination of diluted extract, one can observe small, round, strongly opaque bodies, which cannot be seen in undiluted extract. In precipitated tubes—the dark-field examination shows no distinction between primary precipitation in the Meinicke reaction, and between positive and negative series—there are very few colloidal particles in the extract, while in the nonprecipitation series, or upon

the addition of NaCl to the serum extract mixtures, one can easily see the result of the molecular rearrangement in the growth of the colloidal particles in the positive serums of Phase I Meinicke reaction, and in the Sachs-Georgi reaction. Here and there one may observe a netlike structure in the flocculi, each being strongly opaque, which makes these particles easily seen.

If Joel's and Meinicke's original explanation is correct, namely, that the efficacious colloidal particles take part in the flocculation, then in a positive Sachs-Georgi reaction, serum plus extract after precipitation of formed flocculi should not precipitate upon the addition of more serum; since the lipoids have been thrown down in large numbers during centrifuging. But this is not true, there being as marked a precipitation in the centrifuged tubes after the addition of serum, as in the control tubes. This question, however, needs more study.

The 0.85 per cent salt solution used in the Sachs-Georgi technic is the optimum concentration needed for the precipitation of the globulins for which it is isoelectric. The horse heart extract used in the Meinicke reaction has two optima: one for distilled water, the other for a 2 per cent NaCl solution. The salt solution in no way affects the antigen or seroglobulins. Although it makes no apparent difference whether or not the blood serum is inactivated at 55° C. for one-half hour, all questionable errors such as the complement are done away with. The latter when present, plays no appreciable rôle in the reaction.

The flocculation, as is seen in the Sachs-Georgi reaction, is the result of the union of the serum globulins with the lipoidal antigen and is very similar to the ultramicroscopic colloidal alteration which takes place in the Wassermann system. The degree of flocculation may depend on the amount of serum globulins present in the syphilitic serum which in turn may be due to the degree of irritation resulting from the action of the *Treponema pallidum* on the tissue cells. It becomes evident then, that in the very active cases of syphilis, although the clinical symptoms may not be markedly apparent, there may be an increased amount of globulins present in the patient's serum (Noguchi<sup>65</sup>). These various amounts of increased serum globulins uniting with lipoidal antigen result in flocculations varying from 1 to 4-plus.

In the negative cases, however, the serum globulins found in syphilitic serum are absent, although nonsyphilitic serum may contain an increased amount of globulins. In these negative cases the salt solution may be isoelectric and equimolecular with the serum globulins and is kept in suspension along with the lipoidal antigen resulting in a clear nonflocculating solution.

Heretofore, we have discussed the various contributions presented by different investigators to explain the mechanism of flocculation. We offer the following suggestions in the hope that they may be of some assistance in explaining and clarifying the subject of mechanism of flocculation reaction in syphilis. In this connection it would be of interest to note the reason for the syphilitic serum showing an affinity for nonspecific lipoidal antigens. As has been mentioned above, there are certain conditions in which the serum globulins may be increased over that of normal, if not in a greater percentage than that found in syphilitic serum. A detailed discussion of this question must be left for a later paper, but we can only mention the various factors which probably play a role in this mechanism.

The *Treponema pallidum* as it irritates the tissue cells causes the globulins to become increased, and a toxin is liberated by the *Spirocheta pallidum* which is specific for syphilis. When this occurs the globulins combine with this toxin, thus causing this sensitized globulin to have a greater affinity for the lipoidal extract particle, resulting in colloidal aggregates which appear in positive flocculation reactions. In negative cases, although the globulins may be increased in number, there is no specific syphilitic toxin liberated by the spirochete which may combine with the globulin, and no flocculation can occur. This method of reasoning does not explain the flocculations which occur in nonspecific reactions.

In tuberculosis, for example, we know that the serum globulins are increased in number, and that there is also a specific toxin liberated by the tubercle bacillus. These specific toxins may combine with the globulins in the same manner as the syphilitic toxin may combine with its globulins. Inasmuch as the flocculations occurring in nonspecific reactions are not numerous, it is possible that the sensitized syphilitic globulin has a greater affinity for the nonspecific lipoidal extract than any of the other sensitized globulins



have, but perhaps there may be some other reasonable explanation for this mechanism.

What rôle do electrolytes play in the growth of colloidal particles? When NaCl of a certain concentration is added to the antigen and serum, the globulins and lipoidal extract have a tendency to retain certain quantities of the electrolyte. In the preparation of most inorganic colloids small quantities of the electrolytes are retained by the colloids, and these tend to bring about coagulation (Woudstra<sup>71</sup>). With organic colloids a similar phenomenon may occur which becomes manifest, in this connection, to a greater extent with syphilitic globulins than with nonsyphilitic globulins. The influence of age may also be of some significance in bringing about a greater affinity for these colloids.

In flocculation reactions, certain characteristic phenomena may occur, such as a strong flocculation taking place when the tubes are kept in the incubator at 37° C. at any time between 2 and 24 hours, or after standing at room temperature for 24 hours. In some cases after the flocculation has appeared in the first 24 hours, the flocculi may disappear within the following 24 hours. A similar condition also takes place with the Wassermann reaction (as weak positive reactions). In the latter case, it is the opinion of some serologists that weak positive Wassermann reactions may have been strongly positive during the period of incubation, but that some of the clumped red cells may have undergone hemolysis and gone into solution. The explanation for these occurrences is possibly as follows: A colloidal particle is changed in some way by the addition of the electrolyte resulting in coagulation taking place very early, and in the course of time this union becomes stronger. A change in the state of the colloid may also be brought about by electrolytes where the union of colloidal elements decreases after a certain time giving a weak or a negative reaction.

Colloidal solutions have a characteristic electric behavior which may explain many of their peculiar properties; and the magnitude of the electric charge, which most substances in colloidal solution carry, varies greatly. The syphilitic globulin may be so charged that it has a greater electrochemical affinity for the lipoidal extract, producing flocculations, and in the negative cases, where no flocculation takes place the lipoidal extract and serum globulin may

both contain negative charges and they repel each other, since it is a known fact that oppositely charged colloids precipitate each other. In those cases, where there is a weak or a doubtful reaction, the positive and negative charged colloidal particles are held in a loose combination.

#### CONCLUSIONS

1. A brief résumé of the numerous studies of the Wassermann reaction discloses two schools of thought; (1) That which believes that the Wassermann reaction is an antigen-antibody reaction, and has attempted to modify and simplify this reaction, (2) That school which follows the study of the chemistry of the colloids, and has attempted to show a parallelism between the Wassermann reaction and certain colloidal reactions. The latter has led to the Meinicke and Sachs-Georgi reactions.

2. Many investigators have studied the practical value of the Meinicke reaction (Phase I and II) and have reached the following conclusions: There was 89.2 per cent agreement with the Wassermann reaction; this reaction is in all respects characteristic for syphilis and it is more simple than the so-called Third Modification or the Sachs-Georgi reaction; it cannot be used in spinal fluid; the overlapping of the Meinicke Phase I reaction by the Phase II reaction did not prove of any practical value; the theory upon which the Meinicke reaction is based does not explain the kind of flocculation produced.

3. The Third Modification of the Meinicke reaction is more simple and is therefore recommended. The agreement with the Wassermann reaction is 88.8 per cent. In many cases it is positive earlier, and often remains longer than the Wassermann reaction. When Meinicke's horse heart extract was used all Wassermann positive serums did not flocculate, and it is hoped that the acuity of the reaction, and a better antigen will be reached so that the precipitate can be detected with the naked eye.

4. The Sachs-Georgi reaction has met with the approval of many investigators. The nonspecific reactions are less frequent with this reaction. Our agreement with the Wassermann reaction was 92 per cent, as compared with the general averaged agreement of 91 per cent reported by other investigators.

5. A comparative study of the Sachs-Georgi, Meinicke, and Wassermann reactions gives the Sachs-Georgi reaction an advantage over the Meinicke reaction.

6. None of these reactions can at present supplant the Wassermann reaction but may be used in conjunction with it. Our investigations, as well as those of others, have shown that the Sachs-Georgi reaction becomes positive earlier and remains positive (and also in some treated cases of syphilis) longer than does the Wassermann reaction.

7. In an investigation of animal serums with the Wassermann, Meinicke, and Sachs-Georgi reactions, no parallelism was noted.

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# STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XIX\*

## A STUDY OF FACTORS RELATING TO THE SERUM AND SERUM CONTROL TUBE

BY JOHN A. KOLMER, M.D., PHILADELPHIA, PA.

*From the Dermatological Research Laboratories of Philadelphia*

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SEVERAL factors of practical importance in regard to the collection of serum for complement-fixation tests and the amount to employ in the serum control tube, are worthy of consideration in relation to the standardization of technic. These have been studied under the following divisions:

1. A study of methods for the collection of serum in relation to the results of complement-fixation reactions in syphilis.

2. A study of the age and anticomplementary activity of serum and cerebrospinal fluid in relation to syphilis complement-fixation reactions.

3. A study of the amount of serum and cerebrospinal fluid to be used in the control tubes of the complement-fixation test for syphilis.

This part of our investigation did not include a study of the influence upon the Wassermann reaction of sera collected from persons suffering with jaundice, diabetes, during or immediately after acute alcoholism or treatment with antisyphilitic remedies and so forth, all of which are believed by some serologists to exert an influence upon the reactions; special attention has been given the principles concerning technical factors relating to the collection of serum and spinal fluid and the amounts to employ in the control tube of the test.

### Part 1

#### METHODS FOR THE COLLECTION OF SERUM

Blood for the syphilis complement-fixation test is generally col-

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\*Investigation aided by funds accruing from the preparation of arsphenamine.



lected by venipuncture and usually with aseptic technic; with the introduction of modifications of the Wassermann test requiring smaller amounts of serum, the practice of obtaining blood from the finger has gained wide popularity. With a proper lancet and warming of the hand to insure free circulation of the blood, 2 c.c. or more may be obtained from a finger in a small test tube with comparative ease and is frequently the method of choice with nervous individuals and those having small and difficult veins.

*Comparative complement-fixation tests conducted with sera secured from a number of syphilitic persons from a finger and a vein at the same time and tested within three days, have shown no differences either in a qualitative or quantitative test; the amount of antibody in venous blood appears to be the same as in a mixture of venous and arterial blood from a finger.* The results of quantitative tests with specimens of blood of twelve persons collected from a vein at the elbow and from a finger and tested the following day at the same time, were practically identical and are shown in Table I.

TABLE I

RESULTS OBSERVED WITH BLOOD FROM FINGERS AND VEINS, COLLECTED AT THE SAME TIME

No.	SERA FROM FINGERS						SERA FROM VEINS					
	0.1	0.02	0.004	0.0008	0.00016	Con- trol	0.1	0.02	0.004	0.0008	0.00016	Con- trol
1	4*	4	4	-	-	-	4	4	3	-	-	-
2	4	4	-	-	-	-	4	4	-	-	-	-
3	4	4	3	-	-	-	4	4	4	-	-	-
4	4	4	1	-	-	-	4	4	2	-	-	-
5	4	4	4	-	-	-	4	4	4	-	-	-
6	1	1	-	-	-	-	1	1	-	-	-	-
7	4	4	4	-	-	-	4	4	4	-	-	-
8	3	3	-	-	-	-	3	3	-	-	-	-
9	4	4	2	-	-	-	4	4	2	-	-	-
10	4	4	1	-	-	-	4	4	1	-	-	-
11	4	4	4	-	-	-	4	4	4	1	-	-
12	4	4	-	-	-	-	4	4	1	-	-	-

\*4 = ++++; 3 = +++; 2 = ++; 1 = +.

*If, however, the specimens of blood are kept for more than three days differences may be apparent, that is, sera collected from a finger are more apt to become contaminated with bacteria and develop anti-complementary properties.*

The antibody content of finger and vein blood appears therefore, to be the same and finger blood is just as suitable for the complement fixation test as vein blood, if examined before opportunity is afforded for the acquisition of thermostabile antilysins. If many days must elapse from the time of collection of blood to testing of serum, venous blood is preferable *if collected aseptically*; contaminated venous blood is no better than finger blood, as both may develop antilysins in equal degree.

## Part 2

### AGE AND ANTICOMPLEMENTARY ACTIVITY OF SERUM AND SPINAL FLUID

In the course of serological work, sera are sometimes seoured by centrifuging defibrinated blood immediately after collection; a point of interest was to determine whether the antibody content was the same as that in serum left on the clot for several to twenty-four or forty-eight hours, inasmuch as the complement content seems to be slightly increased by the latter procedure.<sup>1</sup>

In an extensive study of this subject Watanabe<sup>2</sup> has shown that the antibody concerned in the Wassermann reaction exists in the plasma of the blood, and our results with serum secured immediately after bleeding are quite similar, the results of a number of tests being shown in Table II.

Von Wedel<sup>3</sup> has made the interesting observation that sera from

TABLE II  
RESULTS OBTAINED WITH SERA SEPARATED IMMEDIATELY AND AFTER BEING  
LEFT WITH CLOTS FOR TWENTY-FOUR AND FORTY-EIGHT HOURS

No.	SERUM SEPARATED IMMEDIATELY	SERUM LEFT ON CLOT FOR 24 HOURS	SERUM LEFT ON CLOT FOR 48 HOURS
1	++++	++++	++++
2	+++	+++	+++
3	++++	++++	++++
4	+++	+++	+
5	+++	++	++
6	++++	++++	++++
7	++++	++++	++++
8	++++	+++	+++
9	+++	+	++
10	++++	++++	++++
11	++	+	+
12	++++	++++	++++

tuberculous individuals may yield negative or weakly positive tuberculous complement-fixation reactions when tested on the first day after the collection of blood, whereas the same sera gave strongly positive reactions seven days later and continued to give these strongly positive reactions week after week with unvarying regularity. Sera from nontuberculous persons gave negative reactions under similar circumstances and an explanation has not been offered of the results with tuberculous sera.

We have conducted similar experiments with syphilitic and non-syphilitic sera employing our regular technic, but with negative results. Not infrequently portions of serum kept at 6 to 8 C. in a refrigerator for ten or more days yielded somewhat stronger reactions, but these were clearly ascribable to the presence of thermostable anticomplementary substances causing nonspecific complement-fixation reactions, or, to the deterioration of a portion of natural antisheep hemolysin. The results observed with a few sera of a series tested on the first, fifth, and tenth days are shown in Table III.

TABLE III

RESULTS OBTAINED WITH THE SAME SPECIMENS OF SERUM ONE DAY, FIVE DAYS AND TEN DAYS AFTER COLLECTION OF SERA

No.	FIRST DAY		FIFTH DAY		TENTH DAY	
	FRONT TUBE	CONTROL	FRONT TUBE	CONTROL	FRONT TUBE	CONTROL
1	++++	-	++++	-	++++	++
2	+++	-	+++	-	++++	+
3	++++	-	++++	-	++++	-
4	+++	-	+++	-	++++	+
5	+++	-	++	-	++	-
8	++++	-	++++	-	++++	+
9	-	-	-	-	+	+
10	-	-	-	-	-	-

The anticomplementary activity of serum and spinal fluid is of great importance in relation to complement-fixation tests; the exact nature of these antilynsins is unknown, although the investigations of Kyutoku<sup>4</sup> have yielded additional information, the following being taken from his report:

1. Human sera do not develop antilynsins as a result of heating, as may occur with rabbit, dog and mule sera.

2. Sterile human sera may develop thermolabile but not thermostable antilynsins.



3. Human sera contaminated with bacteria or deeply colored with hemoglobin develop thermolabile and thermostabile antilysins.

4. The antilysins of human sera are closely allied with the protein constituents and especially the globulin fraction.

5. Absorption of human sera with barium sulphate, kaolin, charcoal, erythrocytes, etc., removes only a portion of the antilysins; filtration of diluted serum through sterile neutral Kitasato filters was found the only effectual manner for removing the antilysins.

The results of studies of the antilysins in human sera are greatly influenced by the hemolytic system employed; for example, with an antisheep system the presence of natural antisheep hemolysin may exert an important influence due to the presence of this substance in a large percentage of human sera in varying amounts.

The results of our studies conducted with sera collected with ordinary care by venipuncture and with an antisheep system, may be summarized as follows:

1. With *unheated* sera two days old, 0.05 c.c. may cause more inhibition of hemolysis than larger amounts, due to the presence of antilysins the effects of which are overcome by the natural hemolysins in the larger amounts of serum. With *heated* sera, 0.2 c.c. or more may show less inhibition of hemolysis than smaller amounts by reason of the presence and influence of these hemolysins escaping destruction or masking during the process of heating, as shown in Table IV. These results were not observed with all sera because the amount of natural hemolysin varied in different sera but were generally observed as summarized in Chart 1.

TABLE IV

THE PERCENTAGE OF 119 HEATED HUMAN SERA PROVING ANTICOMPLEMENTARY IN AN ANTISHEEP HEMOLYTIC SYSTEM WHEN TESTED IN 0.1 TO 0.25 C. C.

0.1 c.c.	0.15 c.c.	0.2 c.c.	0.25 c.c.
11	9	6	5

2. With a series of *unheated* sera five to seven days old, the anti-complementary effects were about the same with amounts varying from 0.05 to 0.2 c.c. but larger amounts showed less inhibition of hemolysis due to the influence of natural hemolysins. With *heated* sera however, results were different, inasmuch as heating destroyed

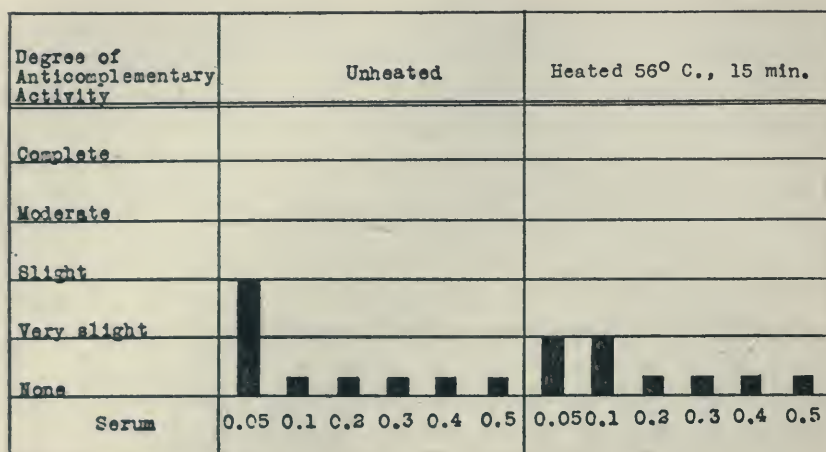


Chart 1.—The anticomplementary activity of sera two days old.

more of the natural hemolysins than anticomplementary substances, so the larger amounts of serum caused more inhibition of hemolysis than the smaller amounts. The balance between antilysins and natural hemolysins varied of course with different sera, but the usual observation is shown graphically in Chart 2.

3. With *unheated* sera ten to fourteen days old, the anticomplementary effects were very marked and generally not influenced by

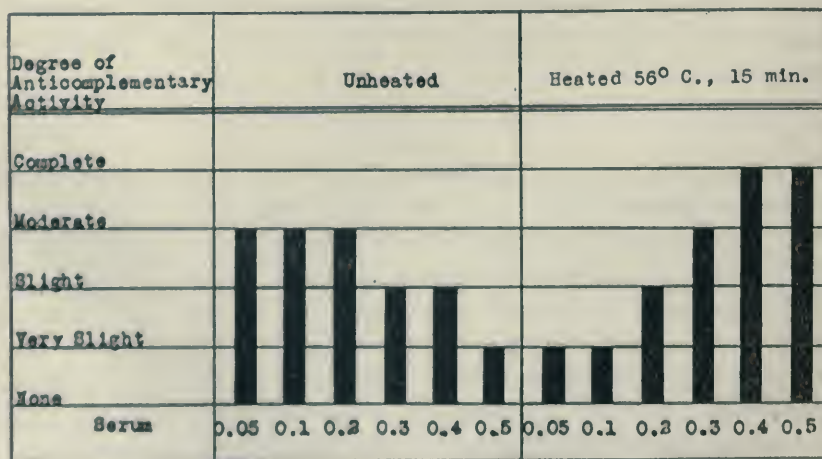


Chart 2.—The anticomplementary activity of sera five to seven days old.

natural hemolysins in even the larger amounts of serum. With *heated* sera the antilysins were more active in the 0.05 and 0.1 c.c. amounts of serum while in the 0.2 and 0.3 c.c. amounts the natural hemolysins gained the upper hand to be overcome again by the antilysins in the 0.4 and 0.5 c.c. amounts of serum. These results are varied with different sera, but Chart 3 presents the usual results.

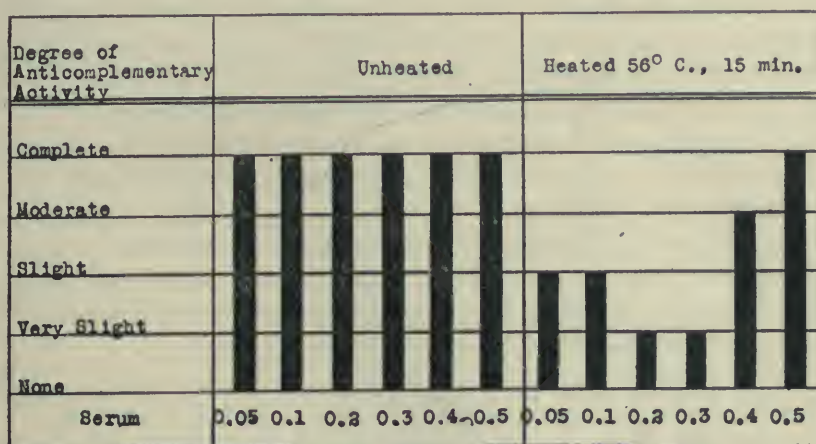


Chart 3.—The anticomplementary activity of sera ten to fourteen days old.

*The influence exerted by the antilysins in human sera causing the anticomplementary action of sera, so designated because the antilysins are believed to interfere with hemolysis by a destructive influence upon hemolytic complement is very much influenced by natural hemolysins and the results are modified by the balance of power between these two substances in any given serum. Both exist in thermolabile and thermostabile forms but the hemolysins are probably more susceptible to heat than the antilysins.<sup>5</sup> With cerebrospinal fluid, the influence of antilysins is not generally so modified because of the absence of natural hemolysins in the majority of fluids, except antishoop hemolysin in the fluids of parietic individuals, or, the hemolysins may be present in but traces and insufficient for influencing the results. Likewise in the antihuman and antichickens hemolytic systems the influence of antilysins in heated sera are not subject to the influence of natural hemolysins to the same degree as in the anti-sheep and antiox systems.*



These antilysins have therefore, an important influence upon complement-fixation reactions and *when specimens of blood and spinal fluid are sent to a laboratory from a distance, permitting the development of thermolabile antilysins, the results of complement-fixation tests must vary in some degree from those conducted with perfectly fresh sera and fluids*; this fact should be kept in mind in judging the merits of a technic and explains in part the differences in degree of positive reactions observed with portions of the same blood of a syphilitic person sent to different laboratories in the same or different cities where methods vary in the care with which the specimens are preserved and guarded against the development of antilysins.

Of course, the results should be identical insofar as positive or negative are concerned; only the *degree of positiveness* should be left open to the influence of antilysins. Any serum or spinal fluid so anticomplementary as to jeopardize the correctness of the positive or negative reaction, should be detected in the serum control tube and ruled out as unfit; this brings up the important question of how much serum and spinal fluid should be used in the control tube.

### Part 3

#### THE SERUM CONTROL TUBE

The object of the serum control tube is to show whether or not the serum or spinal fluid is anticomplementary and to guard thereby against false or pseudopositive reactions, due to nonspecific fixation or destruction of complement by serum or spinal fluid.

Wassermann advised the use of double the amount of patient's serum and spinal fluid, but experience has shown that this caution against anticomplementary effects of serum is frequently defeated by reason of the influence of natural antisheep hemolysin as discussed above. At the present time the majority of workers employing the antisheep hemolytic system as shown in Table V, use the same amount of serum in the control as in the main tube or tubes of the test.

It is easily possible for a larger amount of serum in the control tube to carry sufficient natural hemolysin to overcome the anticomplementary effect of antilysins, result in complete hemolysis and thereby lead to misinterpretation of slight inhibition of hemolysis in the main tubes. As stated by Ottenberg, the real object of a control tube is to

TABLE V

THE AMOUNT OF SERUM USED IN THE SERUM CONTROLS BY VARIOUS AUTHORS

AUTHOR	HEMOLYTIC SYSTEM	SERUM AND ANTIGEN	SERUM CONTROL
Wassermann	Antisheep	0.2	0.4
Citron	Antisheep	0.1 and 0.2	0.2
Browning and McKenzie	Antiox	0.1	0.1
Boas	Antisheep	0.05, 0.1, 0.2	0.2
Thomsen	Antisheep	0.05, 0.1, 0.2	0.2
Ottenberg	Antisheep	0.1	0.1
Kolmer	Antisheep	0.2	0.2
Thomas and Ivy	Antisheep	0.1	0.1
N. Y. Depart. Health	Antisheep	0.2	0.2, 0.4
Field	Antisheep	0.2	0.2
Walker and Swift	Antisheep	0.2	0.4
Kaplan	Antisheep	0.2	0.2
Sorman	Antisheep	0.2	0.2
Neill	Antisheep	0.2	0.4
Noguchi	Antihuman	0.02 or 0.08	0.02 or 0.08
Craig	Antihuman	0.1	0.1
Vedder	Antihuman	0.1	0.15
Simon	Antisheep	0.1	0.1
Lyon and Eiman	Antisheep	0.1	0.1

give an accurate picture of the effect the serum is having in the main tube and for this reason I agree with him that the dose of serum in the control tube should be the same as that in the main tube.

Unfortunately, a serum may contain so small an amount of anti-lysin as to yield a perfect control tube of complete hemolysis and yet show a very slight degree of inhibition of hemolysis in the presence of antigen; this however, can be guarded against in my experience, by certain technical details including the use of a proper amount of antigen and titrating the complement in the presence of antigen.

With the antisheep and antiox hemolytic systems the use of a larger amount of serum in the control tube tends rather to inaccuracy than accuracy; with the antihuman and antichickem hemolytic systems the use of a larger amount of serum or spinal fluid in the control tube tends to greater caution against anticomplementary reactions, but is not absolutely necessary for the sake of accuracy.

## Part 4

### COLLECTION OF BLOOD FOR THE WASSERMANN TEST

It is claimed by some serologists that the blood serum of nonlucetic persons collected during jaundice, certain stages of diabetes mellitus,

during the febrile period of malaria, pneumonia and other diseases, may yield falsely positive reactions; in my experience these reactions are very rare and largely preventable by technical details and especially against anticomplementary effect of serum.

Craig and Nichols<sup>6</sup> have stated that the serum of a luetic individual collected during or immediately after an acute alcoholic debauch may give a falsely negative reaction; several serologists agree with him and I believe it good practice to avoid this possible source of error.

It is commonly and widely believed that the serum of a luetic individual collected during or immediately after intensive specific treatment may yield a falsely negative reaction; I question the accuracy of this statement. In my experience the results are frequently just the reverse, that is, a serum reacts positively when tested during or immediately after treatment and negatively after a period of some weeks or months thereafter during which specific treatment has not been given. At any rate one negative reaction is of little value and the test should always be repeated at intervals over a sufficiently long period to make sure of the correctness of a negative reaction.

Blood collected within an hour after a meal is apt to yield a chylous or milky appearing serum; this does not appear to cause harm insofar as complement-fixation reactions are concerned, although some serologists believe that these sera are particularly apt to prove anticomplementary.

While these matters are worthy of attention and further study in relation to the biology and mechanism of the Wassermann reaction, they do not directly concern the technic of collection of blood for the test; in reference to the latter the following technical details are of value in the interests of the best work:

1. If blood is to be sent a distance or, if for other reasons the serum cannot be tested for four or more days, it should be collected aseptically from a vein in order to guard against bacterial contamination, which results in the development of thermostabile anticomplementary substances (antilynsins).

2. If the serum is to be tested within three or four days of collection of blood and can be kept at a temperature of 6° C. or colder, the specimen may be collected from finger, skin or vein without special precautions against contamination, inasmuch as the interval is not



generally sufficient for the growth of bacteria to render the serum anticomplementary.

3. If the specimen of blood is subject to agitation as in the mails, the container should be of such size as to be filled or almost so with blood, in order to reduce the amount of agitation and consequent hemolysis, inasmuch as an excess of hemoglobin in the serum tends to render it anticomplementary.

Spinal fluids, while collected with aseptic precautions, are not infrequently contaminated with a skin coccus; fortunately they acquire anticomplementary effects rather tardily. *With both blood and spinal fluid regardless of the technic of collection, it is important to keep the specimens at or as near 0-2° C. as possible; this is the most important single safeguard for preservation.*

From the laboratory standpoint, I believe *the serum should be left on the clot until ready for testing unless the interval is so long and the temperature such that hemolysis takes place*; in my experience separated sera are more apt to become anticomplementary than sera on the clots, both being kept and handled under identical conditions.

#### CONCLUSIONS

1. The antibody content of serum from mixed venous and arterial blood collected by pricking a finger, and of venous blood collected by venipuncture, is identical.

2. Blood sera collected from a finger or by cupping are more likely to become anticomplementary than sera collected by aseptic technic and venipuncture, due to greater chances for bacterial contamination.

3. Syphilitic sera collected at once by defibrinating and centrifuging blood contain as much complement-fixing antibody as sera allowed to separate for one to forty-eight hours.

4. When preserved human sera yield a stronger complement-fixation reaction than the same sera while fresh, the difference is due to the presence of anticomplementary substances (antilynsins) or the deterioration of natural hemolysins.

5. The anticomplementary activity of a serum is greatly modified by whether or not it is used unheated or heated and by the presence or absence of natural hemolysins.

6. The presence of anticomplementary substances (antilynsins) influences the degree of positiveness of a reaction and explains in part

the differences observed with portions of the same blood in different laboratories; technic should, however, discover the presence of these antilynsins and render all laboratory reports uniform insofar as positive or negative reactions are concerned.

7. The serum control tube should not carry more serum or spinal fluid than the main tube or tubes if an antishoop or antiox hemolytic system is being employed in order to avoid the influence of natural hemolysins; with an antihuman or antichicken hemolytic system the use of a slight excess of serum and spinal fluid in the control tube serves the purpose of caution, but is not absolutely essential.

8. The guiding principles for the collection of blood and spinal fluid for the Wassermann and other complement-fixation tests, is avoiding or minimizing the opportunities for development of anti-complementary substances (antilynsins) and the occurrence of falsely negative reactions; these principles are presented and discussed.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XX\*

### A STUDY OF FACTORS INFLUENCING THE AMOUNT OF HEMOLYSIN EMPLOYED IN COMPLEMENT-FIXATION TESTS

BY JOHN A. KOLMER, M.D., ELIZABETH YAGLE, AND ANNA M. RULE,  
PHILADELPHIA, PA.

*From the Dermatological Research Institute of Philadelphia*

(Received for publication, November 30, 1920.)

THE amount of hemolysin employed by different serologists in the conduct of complement-fixation tests for syphilis varies to a considerable extent and especially among those using antish sheep and antio x hemolytic systems. A few employ a single unit but the majority use two or more units; apparently all workers employing the antihuman hemolytic system use two units.

#### ERROR DUE TO EXCESS OF HEMOLYSIN

As is now well known an excess of hemolysin under certain conditions may produce complete hemolysis even though a portion of the complement has been fixed by syphilis antibody and antigen, thereby yielding falsely negative reactions with *weakly positive* sera (but not with strongly positive sera); this is especially apt to occur when the tubes are placed in a refrigerator overnight for the settling of corpuscles before the reactions are read. While it is customary to hold this fact as a weighty argument against the antish sheep hemolytic system owing to the influence of natural antish sheep hemolysins, recent studies by Williams<sup>1</sup> have shown that natural antihuman hemolysins may have a similar influence upon an antihuman hemolytic system unless special precautions are taken in the choice of corpuscles.

Allowance for nonspecific fixation of complement by antigen and serum alone is made by using an excess of complement or hemolysin or both; in a previous study of this phase of the problem we arrived

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\*Investigation aided by funds accruing from the preparation of arsphenamine.



at the conclusion that best results are secured by titrating the complement in the presence of antigen and using two units. Under these conditions the proper amount of hemolysin to employ is that which will result in complete hemolysis of all controls and tests with nonsyphilitic sera within the hour of secondary incubation, but fail to produce hemolysis or but partial hemolysis, when the complement has been fixed by syphilis antibody and antigen. In other words *the problem is to avoid an excess of immune hemolysin and neutralize the influence of natural hemolysins for the purpose of detecting the slightest degree of specific fixation of complement.*

The amount of patient's serum employed in a complement-fixation test bears an important relation to the influence of natural hemolysins. In qualitative tests employing a single amount of serum as 0.1 c.c. or 0.2 c.c., the effect of natural hemolysins is a matter of importance, but in quantitative tests employing graded amounts of serum as 0.1 c.c. to 0.001 c.c. in the test proposed as a standardized technic,<sup>2</sup> the influence of the natural hemolysins becomes negligible in all amounts of serum less than 0.1 c.c.

An excessive dose of hemolysin may be harmful both during and after the secondary incubation. It may greatly hasten hemolysis and produce falsely negative reactions with weakly positive sera or at least mask the actual degree of specific fixation of complement when a fixed period of secondary incubation is being used, as one hour in a water-bath. By continuing hemolysis after the secondary incubation the same effects may be produced although these may be prevented by reading the reactions within two or three hours or by the very simple procedure of placing the tubes in a water-bath at 55° C. for ten minutes (not longer) which inactivates all traces of complement and thereby breaks up the hemolytic system.<sup>3</sup>

#### PROCEDURES FOR AVOIDING THE INFLUENCE OF NATURAL HEMOLYSINS

Theoretically at least the best work, that is, the most sensitive specific reactions, require that there should be no natural hemolysins in the patients' sera or complement to interfere with a close adjustment of the hemolytic system.

Routine removal of natural hemolysins from sera would appear to be the only method for obtaining these conditions with an anti-sheep hemolytic system. When but few sera are to be tested absorp-

tion with corpuscles is practical but with large numbers of sera this procedure entails too much work and time; furthermore, absorbed sera should be re-heated to remove antilysins which results in further destruction of syphilis antibody.<sup>4</sup>

Several modifications of the Wassermann test have been proposed for avoiding the influence of natural antisheep hemolysin in human sera during the secondary incubation. Kaliski adds the corpuscles alone and waits for ten or fifteen minutes for hemolysis and adds immune hemolysin only as required. This technic is not suitable however for quantitative complement-fixation tests employing varying amounts of each serum, which is the principle adopted for the proposed standardized technic.

Another method employed by some serologists is to carefully watch each serum control during the secondary incubation and remove the tubes for reading as soon as the controls show complete hemolysis. This practice is suitable for a small number of tests, but when fifty or more sera are being examined at one time it is apt to prove too troublesome.

The influence of natural hemolysin in the complement serum may be adjusted by the simple procedure of titrating the immune hemolysin each day with an *average* amount of complement. If the complement happens to be rich in natural hemolysin a correspondingly smaller amount of immune hemolysin will be found to constitute a unit; if the complement is free of natural hemolysin the unit of immune hemolysin will be correspondingly greater.

#### PURPOSE OF INVESTIGATION

It remains to determine what constitutes the best amount of hemolysin to use in quantitative tests employing graded amounts of serum in order to avoid the effects of an excess *during* a fixed secondary incubation of one hour in a water-bath without employing any of these methods; this was the object of our investigation.

The possible effects of an excess of hemolysin *after* the secondary incubation may be prevented by reading the reactions within two hours instead of placing the tubes in a refrigerator overnight; if, however, the latter procedure is insisted upon to facilitate the readings, the tubes should first be heated in a water-bath at 55° C. for ten minutes to break up the hemolytic system.

## THE UNIT OF HEMOLYSIN

In methods employing a fixed and arbitrary dose of complement as in the original Wassermann test, the unit of hemolysin is easily determined each day by titration with this fixed dose of complement. *In methods employing a titration of complement, the hemolysin should be titrated with the average unit of complement as determined by experience.* Some serologists have apparently overlooked this important detail and determine the "unit" of hemolysin with an amount of complement out of proportion to that used in their complement-fixation tests. Under these conditions what is designated as a "single unit" may actually be more or less than a unit in the main tests.

This is especially true if less than the average unit of complement is employed in the titration. Under these conditions a larger amount of hemolysin must be used for a unit and may represent an excess when employed in complement-fixation tests with larger amounts of complement.

The use of an excessive amount of hemolysin in the complement titration may reduce the unit of complement to such a small amount of serum as to be insufficient for complement-fixation tests even when used in two units, that is, the unit of complement is below the absolute minimum.<sup>5</sup> *In our experience best results have been secured by titrating the hemolysin with an average unit of each complement serum; this is followed by a titration of the complement in the presence of antigen.*

## INFLUENCE OF AMOUNT OF HEMOLYSIN UPON COMPLEMENT TITRATIONS

We believe that it should be a fixed principle that *the hemolysin be used in the same amount for both the complement titration and the main complement-fixation tests.* Some serologists titrate the complement with a fixed amount of hemolysin (one or two units) but use a larger amount of hemolysin with two units of complement in the complement-fixation tests; this practice results in the use of an excess of hemolysin and reduces the sensitiveness of the tests.

In the proposed standardized method the corpuscles are used in 0.5 c.c. of a 2 per cent suspension and the *average* amount of complement used in the hemolysin titration is 0.3 c.c. of a 1:30 dilution. The hemolysin is titrated with the complement serum of each day's work



to adjust for any possible influence of natural hemolysin in the complement serum. The extra work and time involved are almost negligible and more than compensated for by the improvement in results.

The complement is then titrated in the presence of antigen; the question arises how many units of hemolysin should be employed?

If one unit of hemolysin is used the unit of complement represents more serum than if two or more units are employed. If four to six or more units of hemolysin are used the unit of complement is correspondingly smaller and may reach an amount so small that even two units are less than the absolute minimum and entirely unsatisfactory for complement-fixation tests.

As shown in Table I the average unit of fourteen different complement sera\* was 0.26 c.c. of 1:30 dilution when titrated with one unit of hemolysin but 0.2 to 0.19 c.c. when titrated with four or more units of hemolysin. Experience has shown that under these conditions a complement unit of 0.15 c.c. or less serum is unsatisfactory even when used in a dose of two units; as shown in the table the use of four to six units of hemolysin is likely to reduce the unit of complement to this unsatisfactory absolute minimum with a large percentage of complement sera.

Experience has shown that complement-fixation tests conducted

TABLE I

THE INFLUENCE OF ANTISHEEP HEMOLYSIN UPON THE TITRATION OF COMPLEMENT IN THE PRESENCE OF ANTIGEN

COMPLEMENT SERA 1:30	UNITS OF COMPLEMENT WITH			
	1 UNIT HEMOLYSIN	2 UNITS HEMOLYSIN	4 UNITS HEMOLYSIN	6 UNITS HEMOLYSIN
1	0.3	0.3	0.25	—
2	0.2	0.15	0.15	—
3	0.2	0.15	0.15	0.1
4	0.35	0.35	0.3	0.3
5	0.25	0.25	0.25	0.25
6	0.3	0.3	0.25	0.25
7	0.25	0.2	0.2	0.2
8	0.2	0.15	0.15	0.1
9	0.2	0.2	0.15	0.15
10	0.2	0.2	0.15	0.15
11	0.2	0.2	—	0.15
12	0.35	—	—	0.25
13	0.25	0.2	—	0.15
14	0.35	0.3	—	0.25
Average	0.26	0.23	0.2	0.19

\*Each complement serum was a mixture of the sera of three or more guinea pigs.

with two units of complement based upon titrations with one and five units of hemolysin yield the most delicate reactions with anti-sheep and antiox hemolytic systems; both methods, however, are unsatisfactory because of too close adjustment of the hemolytic system and without sufficient allowance for nonspecific fixation of complement by serum alone and antigen alone in the ice box method of primary incubation.

With the antihuman and antichicken hemolytic systems one unit of hemolysin is insufficient because the unit of complement represents too much guinea pig serum and greatly reduces the sensitiveness of complement-fixation tests.

The sum total of a large number of experiments has proved for us that *best results are observed by titrating the complement with two units of hemolysin and conducting the complement-fixation tests with two units of complement and two units of hemolysin.* The reasons for this decision follow.

#### THE INFLUENCE OF HEMOLYSIN UPON COMPLEMENT-FIXATION REACTIONS

This important subject was studied by testing a large number of syphilitic and nonsyphilitic sera in amounts varying from 0.1 to 0.001 c.c.; each serum was employed in these varying amounts in three tests employing the same antigen and same complement (two units) and so forth, but using one, two and five units of hemolysin, respectively, in the three sets. In the first set one unit of hemolysin was used in the complement titration and main tests; in the second set, two units of hemolysin and in the third set five units of hemolysin, were used in the complement titrations and main tests. It is worthy of special attention therefore, that *the complement was titrated with one, two and five units of hemolysin for the respective sets of complement-fixation tests;* different results would have been observed if the same unit of complement had been used in all three sets based upon titration with a fixed amount of hemolysin.

The results have been analyzed under the following three divisions:

1. Influence upon hemolysis of the serum and antigen controls.
2. Influence upon rapidity of hemolysis.
3. Influence upon specific complement reactions fixation.

1. *Influence of hemolysin upon serum and antigen controls.*—In the work conducted with one unit of hemolysin for the complement titra-

TABLE II  
THE INFLUENCE OF THE AMOUNT OF HEMOLYSIN EMPLOYED IN THE COMPLEMENT TITRATION AND FIXATION TESTS UPON THE SENSITIVENESS OF THE REACTIONS AND THE SERUM CONTROLS\*

CONDUCTED WITH 1 UNIT HEMOLYSIN**						CONDUCTED WITH 2 UNITS HEMOLYSIN						CONDUCTED WITH 5 UNITS HEMOLYSIN					
0.1	0.02	0.00	0.001	0.001	Con- trol	0.1	0.02	0.001	0.002	0.001	Con- trol	0.1	0.02	0.001	0.002	0.001	Con- trol
3***	2	1	-	-	1	3	1	-	-	-	-	3	2	1	-	-	1
4	3	2	1	-	1	4	1	-	-	-	-	4	1	-	-	-	1
4	3	1	-	-	1	4	1	-	-	-	-	4	1	-	-	-	1
4	3	1	-	-	1	4	4	1	-	-	-	4	4	1	-	-	1
4	3	1	1	-	1	4	3	1	-	-	-	4	4	1	1	-	1
4	3	1	1	-	1	4	3	1	3	-	-	4	4	3	3	-	-
4	4	4	2	-	1	4	4	4	-	-	4	4	4	4	-	-	4
4	4	4	1	-	1	4	4	4	-	-	-	4	4	-	-	-	-
4	4	3	1	-	1	4	4	4	-	-	-	4	4	-	-	-	-
4	2	1	-	-	1	2	1	-	-	-	-	2	2	1	-	-	1
4	2	1	-	-	1	4	-	-	-	-	-	4	-	1	-	-	1
3	1	-	-	-	1	2	-	-	-	-	-	3	-	-	-	-	1

\* Picked sera more than four days old and containing slight amounts of thermostable antilyns.  
\*\* Unit of complement with one unit of hemolysin was 0.3 c.c. of 1:30; with two units of hemolysin 0.25 c.c. and with 5 units of hemolysin 0.2 c.c.  
\*\*\* 4 = + + + +; 3 = + + +; 2 = + +; 1 = +



tions and main complement-fixation tests, the percentage of reactions showing incomplete hemolysis of the serum and antigen controls was highest and least in reactions employing two units of hemolysin for the complement titrations and main tests. Five units of hemolysin gave fewer of these anticomplementary reactions than observed with one unit of hemolysin but more than observed with two units. These observations are brought out in Table II, but we are not able to express the differences in percentages.

If the serologist could always use perfectly fresh sera, one unit of hemolysin for the complement titration and main tests would be satisfactory, but if older sera must be used and if he insists upon *perfectly hemolyzed controls*, best results eventually follow the use of two units of hemolysin. It is emphasized that these observations are based upon a primary incubation of eighteen hours at 8° C. which increases the degree of nonspecific fixation of complement by sera and antigens alone as well as by mixtures of these.<sup>6</sup>

2. *Influence of hemolysin upon the rapidity of hemolysis in the controls.*—A study of this subject necessarily influences the question of duration of secondary incubation which is discussed in a separate communication.<sup>7</sup> Probably all serologists prefer a secondary incubation of one-half to one hour and clear, sparkling controls of complete hemolysis.

With one and five units of hemolysin for the complement titrations and main tests the controls of some sera require more than an hour for complete hemolysis; hemolysis with one unit is usually slower than with five units and quickest with two units as shown in Table III. Very rapid or "explosive" hemolysis which some serologists desire, are apt to reduce the sensitiveness of reactions with weakly positive sera, but fairly rapid hemolysis which is complete in one half to one hour appears to be desirable and yields very delicate reactions if read within two or three hours after removal from the water-bath. The use of two units of hemolysin for complement titrations and complement-fixation tests with antisheep, antiox and antihuman hemolytic systems has been found generally satisfactory.

3. *Influence of hemolysin upon specific complement fixation.*—With antisheep and antiox hemolytic systems the most sensitive reactions were usually observed when the complement was titrated and the complement-fixation tests were conducted with one unit of hemolysin.

TABLE III

THE INFLUENCE OF ANTISHEEP HEMOLYSIN UPON THE RAPIDITY OF HEMOLYSIS IN SERUM CONTROLS

SERUM	COMPLETE HEMOLYSIS IN MINUTES		
	1 UNIT HEMOLYSIN	2 UNITS HEMOLYSIN	5 UNITS HEMOLYSIN
1	120	60	120
2	15	35	40
3	35	25	110
4	45	40	30
5	15	10	10
6	15	15	10
7	30	25	30
8	20	10	10
9	120	60	90
10	90	30	20
Average	50	31	47

If it were not for the fact previously discussed that the serum controls not infrequently show incomplete hemolysis with one unit of hemolysin, the use of a single unit would be the method of choice with these hemolytic systems. With an antihuman system a single unit is distinctly unsatisfactory because it raises the unit of complement too high unless a very good hemolysin is used and likewise results in many unsatisfactory controls.

A very large number of comparative tests have been required in order to reach a decision on the best amount of hemolysin to employ. Each serum was tested in five amounts varying from 0.1 to 0.001 c.c. with one to ten units of hemolysin for the complement titrations and main tests.

The results are summarized in Table IV and Chart 1 by averaging the degree of complement fixation with the five amounts of each serum in each set of reactions. For example, if a serum gave a + + + +, + + +, + +, + and - reaction the average was secured by adding the pluses and dividing by five which in this example gives 1.8. The highest possible degree of complement fixation in this scheme would be 4 but this seldom occurs as but few sera contain enough antibody to give a + + + + reaction with 0.001 c.c. or less serum in the technic employed.

All the reactions were read two or three hours after a fixed period of one hour secondary incubation. The differences in degree of complement fixation with the different amounts of hemolysin were not considerable and occurred only with the smaller amounts of serum.

TABLE IV

THE INFLUENCE OF ANTISHEEP HEMOLYSIN UPON THE DEGREE OF COMPLEMENT FIXATION

EXPERIMENT	DEGREES OF COMPLEMENT FIXATION WITH HEMOLYSIN				
	1 UNIT	2 UNITS	4 UNITS	6 UNITS	10 UNITS
1	2.5*	2.4	2.3	-	-
2	3.1	2.9	2.7	-	-
3	2.2	-	-	2.0	-
4	2.5	2.3	2.4	-	-
5	2.7	2.4	2.3	-	-
6	2.4	2.5	-	2.5	-
7	2.8	2.8	2.1	2.3	2.1
8	2.3	2.2	2.0	2.0	1.9
9	2.6	2.4	2.2	2.2	2.3
10	1.9	2.1	-	2.1	-
11	2.3	2.0	2.0	2.0	2.0
12	3.2	3.0	3.0	2.8	2.8
13	2.4	2.4	-	-	2.0
14	2.3	2.3	2.4	-	-
15	2.3	2.0	1.6	1.7	2.0
Average	2.5	2.4	2.3	2.2	2.2

\*See text for explanation.

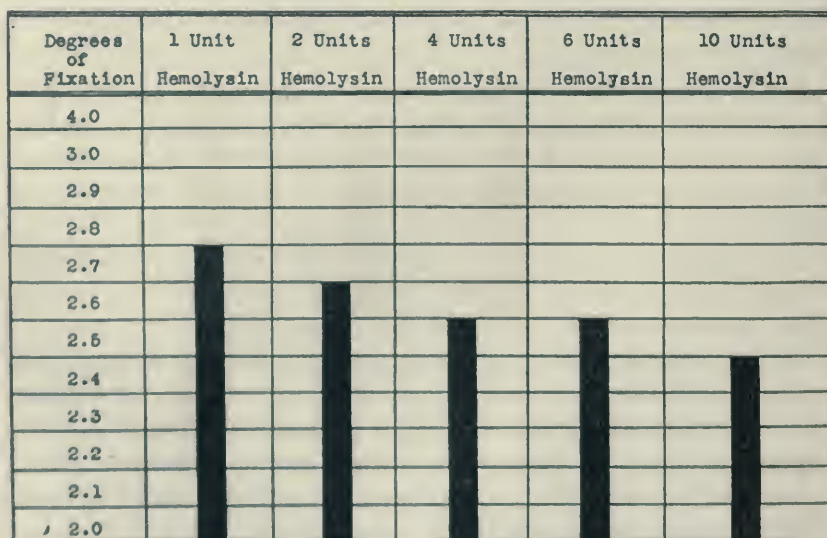


Chart 1.—The influence of antisheep hemolysin upon syphilis complement-fixation tests when the results were read within two hours after the secondary incubation.



When the tests are set aside overnight in a refrigerator before the readings are made, the reactions were usually (not always) slightly more sensitive with one and five units of hemolysin than with two units as shown in the results of one experiment with twenty-five sera summarized in Chart 2. The reason is due to the fact that with one unit of hemolysin there is a very close adjustment of the hemolytic system minimizing the influence of natural hemolysins in the sera; with five units of hemolysin in the complement titration and main tests, the unit of complement is considerably reduced which also results in a very close adjustment of the hemolytic system.

Degrees of Fixation	1 Unit Hemolysin	2 Units Hemolysin	5 Units Hemolysin
4.0			
3.0			
2.8			
2.6			
2.4			
2.2			
2.0	■		■
1.8		■	
1.6			
1.4			
1.2			
1.0			

Chart 2.—The influence of antishcep hemolysin upon syphilis complement-fixation tests when the results were read twenty-four hours after the secondary incubation.

While the most sensitive reactions resulted when the complement was titrated and the main tests conducted with one unit of hemolysin, in order to avoid nonspecific reactions and unsatisfactory controls we have concluded that *best results are secured when two units of hemolysin are used for the complement titrations and main tests. The differences in sensitiveness of reactions are very slight and the results are uniformly more satisfactory.*

## CONCLUSIONS

1. It is advisable to titrate the hemolysin each time complement-fixation tests are conducted in order to make proper adjustment for the presence of natural hemolysins which may be present in the complement serum.

2. In titrating the hemolysin the amount of complement employed should be neither too large nor too small but represent an average unit based upon experience.

3. The same amount of hemolysin should be used in the complement titration and complement-fixation tests; under these conditions the most sensitive reactions occur when one or five units of hemolysin are used. The use of these amounts of hemolysin may, however, result in too close adjustment of the hemolytic system yielding unsatisfactory controls.

4. Best results were observed with antishoop, antiox, and antihuman hemolytic systems when the complement was titrated and the complement-fixation tests conducted, with two units of hemolysin.

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## SPINAL PUNCTURE IN DIAGNOSIS AND TREATMENT\*

BY CARL H. BASTRON, A.M., M.D., LINCOLN, NEBR.

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**I**NDICATIONS for spinal puncture can be classified into two groups as diagnostic and therapeutic. It is not the intention to enumerate all the conditions that have been advocated as indications for spinal puncture, but rather to review the current opinions on the subject of spinal puncture, and question some of the indications advocated as therapeutic entities.

The literature on this subject is very abundant, and the indications advocated for the employment of spinal puncture are as various as they are numerable. The most valid indications are no doubt the simple meningitides, conditions accessible for diagnosis and amenable to treatment almost entirely by means of the cerebrospinal fluid. With the exception of drainage in various pathologic conditions of the central nervous system, this is practically all that can be claimed for spinal puncture as of unquestionable value therapeutically; whereas on the diagnostic side the procedure finds a large and legitimate field of usefulness.

In the diagnosis of disease spinal puncture finds legitimate application only when there are sufficient indications that by its employment a diagnosis can be arrived at or materially aided. To perform spinal puncture in a routine manner, or even without sufficient indications of its aid in diagnosis, is wanton practice.

As said before, the value of spinal puncture in the diagnosis of meningitis is unquestioned. It is the most dependable, direct, and practical diagnostic aid we know of in this disease. Its diagnostic value in meningism has been affirmed by Gillette<sup>1</sup>; in meningeal hemorrhage of the newborn by Brady<sup>2</sup>; in carbon-dioxide poisoning by Legry and Lermoyez<sup>3</sup>; and in shell-concussion of the nervous system by Mestrezat<sup>4</sup>. Raventos<sup>5</sup> claims that spinal puncture has benefited pediatrics more than any other field of medicine. Big-

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land<sup>6</sup> urges the employment of spinal puncture in all cases having nervous symptoms. In epidemic encephalitis the procedure has proved of practically no diagnostic value <sup>7, 8, 9.</sup>

Spinal puncture is claimed to be of great diagnostic value by many syphilographers in early syphilis. They base this claim on the contention that syphilis invades the central nervous system very early, and that dire consequences can be prevented by performing spinal puncture in every case of syphilis and instituting a different form of treatment in cases having abnormal spinal fluids. Stuart<sup>10</sup> cites a case of cerebral involvement nine weeks after the institution of treatment and eleven weeks after the appearance of the chancre. The patient had received what would ordinarily have been considered an adequate course of treatment. Vigorous systemic treatment was followed by marked improvement of the cerebral complication. It appears evident to me that had the vigorous treatment been given at the beginning, instead of merely what would ordinarily be considered adequate treatment, the case would not have gone on to cerebral involvement. Scott and Pearson<sup>11</sup>, claim that the *Treponema pallidum* invades the nervous system at a very early stage, and that this can be determined by the examination of the spinal fluid. They advocate spinal puncture in the early part of treatment. They hold that every case of neurosyphilis is primarily an involvement of the meninges, and that the *Treponema pallida* die out in this situation while at the same time they produce degenerative changes in the parenchyma. Morrison<sup>12</sup> agrees with them that the nervous system may become involved at a very early stage of syphilis without giving definite symptoms or signs. Authorities are practically unanimous in urging that no case of syphilis be discharged as cured without one or more spinal fluid examinations. In a series of 91 cases of early syphilis, all giving a four-plus serum reaction, but none a four-plus spinal fluid reaction, McIver<sup>13</sup> found a slight increase in lymphocytes in the majority of cases. But he does not deem it reasonable to conclude that we can determine by the examination of the spinal fluid who is going to develop neurosyphilis. On the other hand, Fieldes, Parnell and Maitland<sup>14</sup> in 624 cases of syphilis, the majority in the early stage, found only moderate pleocytosis in 18 per cent, slight (6 to 9 cells) in 12 per cent. In 168 of their cases with primary syphilis 15 showed definite, 17 doubtful, pleocytosis. In late neuro-

syphilis the diagnostic value of spinal puncture is beyond question<sup>15, 16</sup>.

A somewhat unique indication for spinal puncture has recently been advocated by Dandy<sup>17</sup> in roentgenography. He states that by substituting air for cerebrospinal fluid all parts of the subarachnoid space can be clearly seen in the roentgenogram. By its use one can determine whether a case of hydrocephalus is of the communicating type or not.

As soon as we become sponsors for a certain cause, we direct our chief efforts toward bringing out the favorable points of that cause, ignoring or minimizing the unfavorable ones. Most spinal puncture advocates find themselves in such a position. They either ignore altogether, or greatly minimize, the discomfort and often the acute suffering spinal puncture victims must endure. The greater part of this suffering is the intense headache often following the puncture, and lasting from three to seven days with undiminished intensity on the patient's getting up. The headache is no doubt due to the loss of spinal fluid, but a good many cases proved puzzling on this explanation, because only a few mils<sup>18, 13</sup> of fluid had been withdrawn, until McRoberts<sup>18</sup> advanced a theory which seems to account for all cases. He says that the dura, being a stiff membrane without contractile tissue, retains the puncture made by the spinal needle for several days, and the spinal fluid, normally always being under some pressure, leaks away through this puncture hole as long as the latter remains unclosed. The fluid thus depleted, the brain loses its supporting fluid cushion; the basilar plexus of veins is pressed upon and this causes a venous congestion of the brain. The sudden onset of severe headache when the patient sits up is due to the sudden rise of intracranial pressure caused by the rise of pressure in the cerebral veins. In the course of a week the puncture hole heals, the fluid is rapidly replenished, and the headache is gone.

Besides these temporary and withal not serious effects, there is a real danger which cannot be too strongly urged against the indiscriminate use of spinal puncture. This is brought out by Weed, Wegforth and Ayers<sup>19</sup>, who succeeded in producing meningitis in cats and other animals by withdrawing spinal fluid shortly after intravenous injections of *B. mucosus capsulatus*, the control animals not developing meningitis. Wegforth and Latham<sup>20</sup> cite five instances in man where infection of the meninges occurred following the re-

lease of normal spinal fluid during septicemia. It may be forcing an analogy where none exists, to compare, in this respect, syphilis and acute meningitis; yet, both are primarily septicemias, and both are prone to lodge in the meninges. Even if the danger of a spirochetal meningitis is not as great as of a bacterial following spinal puncture in the septicemia stage, still the danger exists and should be reckoned with. Perhaps it is because they realize that this danger exists that at the Washington University Dispensary<sup>21</sup> they do not perform spinal punctures on syphilitics until they have obtained two negative serum Wassermann tests, and that Scott and Pearson<sup>11</sup> administer two doses of salvarsan before they test the spinal fluid.

The fact remains, however, that by the examination of spinal fluid in early syphilis cases of neurosyphilis will be detected which would otherwise be overlooked. The present status of intraspinal therapy in neurosyphilis is so uncertain that the argument for spinal puncture in early syphilis, namely, to treat neurosyphilis at its inception, does not sound as convincing as we should wish, for it means nothing to the patient to diagnose his condition without thereby improving the prospects for a cure. Nor has it been shown that systemic treatment is inadequate when given to the limit of tolerance and over a long period of time, with rest periods as may be necessary. The argument for intraspinal therapy rests wholly on clinical results, and very often it is given the entire credit for improvements which might as well be credited to the systemic treatment always given at the same time, and to the incidental spinal drainage. In this connection H. G. Mehrtens<sup>22</sup> found from clinical results of 1500 treatments for neurosyphilis, that intramuscular and intravenous therapy was sufficient in 40 per cent of his cases; of the remainder 35 per cent were benefited by intraspinal therapy, and 15 per cent improved but not arrested. Mark A. Schoenberg<sup>23</sup> is certain from his experience with certain types of optic atrophy, that intraspinal therapy offers better results than the general treatment alone. Scott and Pearson<sup>11</sup> have much confidence in intraspinal therapy, but say that it should always be combined with systemic treatment. They inject, dissolved in the patient's serum, from 0.1 to 0.5 mg. salvarsan. Chas. R. Humboldt<sup>24</sup> prefers the Swift-Ellis method, the technic of which he also adopts for the administration of mercury intraspinally. He claims good results and thinks that the statement that intraspinal therapy possesses nothing superior to the time-honored intensive method is not



borne out by experimental and clinical data. Philip C. Jeans<sup>25</sup> realizes that the rationale and efficacy of intraspinal therapy is in dispute, and that some of the arguments in its favor are founded on insufficient evidence. But he uses intraspinal medication and has no regrets. Channing R. Frothingham<sup>16</sup>, basing his claim on the works of Swift, Walker, Hasler and others, says that in neurosyphilis the type of treatment differs from that which would be used were the central nervous system not involved. Fordyce<sup>26</sup> says that treatment by the usual channels in neurosyphilis may control the symptoms, but seldom cures the infection. An experience of seven years in the use of intraspinal therapy convinces him that practically all cases of early neurosyphilis can be cured more rapidly, and in the majority of cases only cured, by the combined intravenous and intraspinal method.

Many more authors might be cited in favor of intraspinal therapy without adding new arguments or strengthening the ones already presented. I shall now quote a few authors on the negative side of the question. Francis X. Dercum<sup>27</sup> states that attempts at medication of the brain and cord through the subarachnoid space, as in the Swift-Ellis method, are unscientific, as substances introduced into the cerebrospinal fluid disappear rapidly by passing out through the arachnoidal villi and the lymph spaces without in the slightest degree penetrating the nervous parenchyma; that the beneficial effects ascribed to the Swift-Ellis and kindred methods are due entirely to the spinal drainage. Hassin<sup>28</sup> arrives at the conclusion that intraspinal therapy in cases in which especially the parenchyma of the brain is deeply involved, as in paresis, has no physiologic support. When the trouble is in the subarachnoid space (cerebrospinal meningitis), injections in suitable doses produce results. But as used in intraspinal therapy (fractions of a grain of arsphenamin) therapeutic results can hardly be expected. Hassin believes that the favorable reports of the Swift-Ellis treatment can be explained, not by the action of the intraspinal injections, but by that of the intravenous ones.

That neuro-relapses in syphilis, after systemic treatment, are common cannot be questioned, and it is evident that to the extent to which these relapses occur, to that extent is systemic treatment a failure. But whether this failure is inherent in the systemic method of treatment, or due to insufficient treatment, is an open question.

That cases yield to intraspinal treatment which were not influenced by systemic treatment neither establishes the efficiency of the former nor discredits that of the latter. It is probable that these failures are due to insufficient treatment. And this probability is strengthened by the favorable reports we are beginning to receive on silver salvarsan. Kreiblich<sup>29</sup> and Selley<sup>29</sup> have not seen nervous relapses after silver salvarsan. Galewski and Sinn each report one case. In more than 800 cases the records of Walson<sup>29</sup> do not show a case of neuro-relapse. Dreyfus<sup>29</sup> reports good results in early neurosyphilis; the subjective symptoms disappeared after a few injections, and the objective symptoms in one or two weeks. Hahn,<sup>29</sup> Galewski,<sup>29</sup> and Goldberger<sup>29</sup> all report good results in neurosyphilis, both early and late.

Very little of positive value can be said about the curative influence of spinal drainage in neurosyphilis. Derecum<sup>27</sup> claims good results from its employment, while Fordyce<sup>26</sup> says it is valueless. The safest course to pursue at present is to withhold judgment and await further developments. This only applies to spinal drainage as used in the treatment of neurosyphilis. There are many other affections of the central nervous system in the treatment of which the withdrawal of cerebrospinal fluid is clearly of value. In skull wounds Boutier and Logre<sup>30</sup> think that the unilateral vascular disturbances liable to follow injury of the brain may be favorably influenced by spinal puncture. F. Albert<sup>31</sup> claims that lumbar puncture is indicated in the treatment of concussion of the brain, fracture of the base of the skull, and in all cases of irritation of the cortex with increased secretion. Lerda<sup>32</sup> applied spinal puncture in over one hundred cases of pressure of the brain after war wounds, noting the spontaneous subsistence of brain hernias. J. M. Brady<sup>2</sup> employs spinal puncture in suspected cases of meningeal hemorrhage in the newborn. Bambaren<sup>33</sup> advises early lumbar puncture in every case of severe and persisting headache. Mingazini<sup>34</sup> has been employing the procedure in the treatment of what he calls persisting hemi-crania, the headache persisting for months or years. A definite cure was realized in 50 per cent of his cases. In three cases observed by Spiller and de Schweinitz<sup>35</sup> removal of spinal fluid had a remarkable effect on swelling of the optic nerve. Musser and Hufford<sup>36</sup> find that lumbar puncture offers a ready aid in controlling the delirium of lobar pneumonia. Lumbar puncture has also been found of value in controlling delirium tremens. H. V. Pike<sup>37</sup> made observations on

25 cases at the Danville State Hospital for the Insane. Cases of status epilepticus responded promptly to spinal drainage. Epileptic furor or mania showed marked benefit. Complete drainage following apoplectiform convulsions in paretics was followed by a clearing up of the paralysis and a return to the usual mental conditions in 24 hours. Complete drainage within a few hours of the stroke in cerebral arteriosclerosis with thrombosis and hemorrhage has been very encouraging: the patient is rendered more comfortable, the blood pressure is lowered, and life has been prolonged. In manic depressive insanity, with marked clouding of consciousness and psychomotor excitement and intracranial pressure, withdrawal of fluid lessened confusion and decreased excitement. High general arterial pressure was lowered in all cases following complete drainage.

In epidemic encephalitis Llewellys F. Barker<sup>38</sup> found lumbar puncture, done for diagnostic reasons, relieved the symptoms so markedly, that it was repeated at intervals as a therapeutic measure.

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## THE DIAGNOSIS OF SYPHILIS\*

BY H. H. HAZEN, M.D., WASHINGTON, D.C.

*Professor of Dermatology and Syphilology, Georgetown University, Professor of Dermatology and Syphilology, Howard University.*

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ONE rule which the author attempts to impress upon his students is the following: Be quick to suspect syphilis; be slow to diagnose syphilis. For the past ten years there has been entirely too great a tendency upon the part of the medical profession at large to make this diagnosis upon insufficient evidence. Each week patients are seen who have been told that they must have a course in arsphenamine, sometimes for Pityriasis rosea, sometimes for some minor skin affection—(only the day that this was written a patient with ringworm narrowly escaped antisyphilitic treatment) and sometimes upon the rather scanty evidence of a single weak Wassermann reaction. Entirely too much stress has been placed upon the Wassermann by the average practitioner; the old kodak advertisement has been replaced in medicine by "The Wassermann will make the diagnosis, 606 will do the rest." Now as a matter of fact, the diagnosis of this disease is often an extremely difficult one and there are at least twenty-five different procedures which may be helpful in establishing a correct diagnosis. Of these procedures there are very few which taken *singly* will absolutely establish a diagnosis. These will be dealt with later. There exists at present no comprehensive outline for the diagnosis of syphilis. Stokes<sup>1</sup> has published a brief schedule, extremely valuable and suggestive, but it has not as yet been developed in print.

The following procedures are all of value in making a correct diagnosis.

(1) The personal history of the patient must always be accepted with much caution. Many patients will intentionally attempt to deceive the physician, and others are totally ignorant regarding the real nature of their trouble. It is well recognized that the initial and secondary stages of syphilis may be so slight that the real nature of the condition is unsuspected.

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(2) The history of the family or associates may or may not be helpful for the reasons mentioned above.

(3) The examination of the family or associates may or may not throw considerable light upon the case in question. For instance, if a man who has a suspicious lesion has consorted with a woman who has a definite active syphilitic infection, there is good reason to suspect that he has acquired syphilis. If a mother has active syphilis, a newborn child may reasonably be thought to have the same trouble.

(4) The physical examination of the genitals must never be neglected. There may be a superficial sear resulting from an old lesion, or there may be a chancre in some well concealed portion of the body; for instance, in the tonsil, or cervix.

(5) Examination of the skin and mucous membrane is extremely important. During the fulminating stage an experienced dermatologist can frequently absolutely diagnosis syphilis at a glance. Examination of the mucous membranes is extremely suggestive. Sometimes there are late lesions in the throat which are clinically characteristic, but the mucous patches may be successfully imitated by Vincent's angina, or herpetic vesicles.

(6) Routine examination must be made of the bones, especially the tibiae and clavicles, the joints, lymph nodes, the spleen, the liver, the eyes, the ears, the teeth and the testicles. In cases of suspected congenital syphilis changes in the joints, Hutchinson's teeth and Mulberry molars<sup>2</sup> must be searched for.

(7) In special cases examination of certain organs must be made; for instance, stricture of the rectum or esophagus may be due to either cancer or lues.

(8) A cardiovascular examination is of great importance. It is now generally recognized that syphilis is very prone to attack both the heart and larger arteries, although other vascular organs may also be affected. The prevention of aortitis, aneurysm, myocarditis, angina pectoris, and aortic insufficiency is one of the gravest and least recognized problems of the syphilologist of today.

(9) Neurologic examination is of the most importance, for by it we are usually enabled to suspect involvement of the central nervous system. There is, of course, almost no limit to a complete nervous examination, but such a one is usually not required as a routine in syphilis. The eyes must be carefully noted. Examination of the pupils for size and inequalities, always remembering that normal eyes may not react to light and accommodation alike, the abdominal muscle

and cremasteric reflexes, the knee kick and the tendo achillis must be tested. The simple tests of sensation may be important. The test of coordination and the Romberg will suffice as a routine.

(10) A special examination by a skilled ophthalmologist will at times reveal syphilis in unusual cases. Even when examination of the spinal fluid is negative, the alert eye man may recognize signs of trouble. During the work on one of the Medical Advisory Boards, I was very much struck by the fact that the ophthalmologist upon this Board recognized the existence of syphilis in practically every patient where I suspected it, and that in addition, he unearthed many more cases which were negative to a rather hasty general physical examination.

(11) Examination of the ear even by an expert is usually not of striking value from a diagnostic standpoint.

(12) A cystoscopic examination not infrequently reveals the signs of an oncoming tabes.

(13) The Wassermann reaction and its various modifications could be talked about almost indefinitely. The report of the Committee on Diagnosis and Treatment of Syphilis of an All-American Conference on Venereal Diseases<sup>3</sup> may be followed. A digest of this report is as follows: A frank reliable positive blood Wassermann reaction is evidence of syphilis with the following limitations:

(a) In the absence of all other evidence of syphilis a diagnosis based upon a positive Wassermann alone should be made with great caution, and the reaction should be repeated and verified at the hands of other observers.

(b) Weak or partial positive reaction cannot be accepted as diagnostic, but may warrant further investigation.

A negative Wassermann test cannot be regarded as evidence of absence of the disease, although such a negative finding is rare during the secondary stage.

The use of cholesterinized antigens, ice box fixation and certain other modifications which make it extremely sensitive may be of some value in determining treatment, but even these have been challenged. One thing that must be emphasized is that the finding of a negative Wassermann reaction is by no means a sign that treatment should be discontinued.

(14) The luetin reaction is now little used; this is because it has been proved that the ingestion of certain substances, notably potassium iodid will cause a false positive.

(15) The examination of the spinal fluid will at times prove positive in the absence of all other signs. A complete spinal fluid examination includes cell count, examination of the globulin, Wassermann reaction in various dilutions, and the gold chloride curve.

(16) A positive dark-field examination is absolutely diagnostic in cases of primary lesions but must be used with care when the lesions are located within the mouth.

(17) The use of the stains instead of the dark field is sometimes employed, but is not so good.

(18) The animal inoculation with suspected material may prove valuable as Engman's<sup>4</sup> work would seem to indicate. It is also possible that in the future we shall have to determine with what strain a person is infected.

(19) By the modified Levaditi stain, thanks to Warthin's<sup>5</sup> new method, it is possible to find organisms within forty-eight hours. This should be a great diagnostic boon.

(20) The histologic examination of suspicious tissue, examined by a pathologist who *knows* the pathology of syphilis will give a correct diagnosis in many instances. It should be especially noted that in suspected cases the histologic examination of the placenta and umbilical cord affords the promptest method of diagnosing congenital syphilis.

(21) Roentgen ray examination will frequently reveal a characteristic periostitis. In a recent article<sup>6</sup> it has been shown that the x-ray pictures of the bones in congenital syphilis will frequently enable one to make a probable diagnosis.

(22) Special examination of various organs according to approved laboratory methods to determine the pathology of particular organs may be necessary.

(23) Even now the old therapeutic test must occasionally be used.

(24) Operation may have to be used in diagnosis, as in cases of syphilis of the stomach.

(25) Autopsy is the last word in diagnosis.

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## COMPLEMENT-FIXATION TESTS WITH TWO ANTIGENS

### COMPARISON OF RESULTS OF A SERIES OF ROUTINE PUBLIC HEALTH COMPLEMENT-FIXATION TESTS FOR SYPHILIS WITH TWO ANTIGENS

BY MAE E. LARKIN, M.S., SEATTLE, WASHINGTON

*Director Laboratory of the Washington State Board of Health*

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IN AUGUST 1918 the complement-fixation test for syphilis was introduced as a routine procedure in the Laboratory of the Washington State Board of Health. During the year 1918, 435 specimens were received for examination, during 1919, 1827 specimens and during 1920, 7099 specimens. Wherever possible each serum was tested with two antigens, a crude alcoholic and a cholesterinized extract. It seemed that it might be of interest to tabulate the results which were obtained in order to show the percentage of tests which agreed and the percentage which disagreed with the two antigens. The original aim was to show also the number of cases in which the laboratory results could be correlated with the clinical history. It was hoped that the study might support the conclusion which we feel is warranted, that a large proportion of the tests disagreeing with the two antigens could be shown to occur in those cases that had undergone treatment and in which a previous positive result had been obtained. This attempt has been in a measure abandoned, due to the fact that it was impossible to obtain valuable histories in the majority of cases. In a certain number of instances where it appeared that the information available might be of value, this has been made use of as will be shown in the tables and in the text.

#### SCOPE OF WORK

The present paper embraces a total of 5927 specimens which were examined during about two years beginning in August 1918. Being routine public health tests there is a wide variety in the source of specimens. Many are from the public institutions of the State of Washington. It is well recognized that the syphilis complement-

fixation test in a public health laboratory is a different problem than in almost any other laboratory. Specimens are collected by physicians who are largely unfamiliar with the technic of the test. No attempt may be made to preserve the sterility of the blood which is sometimes collected in a container of even doubtful cleanliness. Histories are vague and indefinite if not altogether lacking. Mail service often prolongs the period in transit to a point where the reliability of the reaction is questionable. Hence, many methods in use in clinical laboratories are not adaptable for routine use in the public health laboratory, and the need for a reliable standardized technic cannot be too strongly emphasized.

The technic used in the Laboratory of the Washington State Board of Health is essentially that which has been used in the Laboratories of the New York City Department of Health and published in Park and Williams "Pathogenic Microorganisms."

#### TECHNIC OF THE TESTS

All tests were made with two antigens, a crude alcoholic extract of beef heart and a cholesterinized extract of guinea pig or beef heart. With the greater number of tests the cholesterinized extract of beef heart was used. The antigens were standardized so that the dose used is not more than one-half the anticomplementary dose, provided also that it is twice the smallest fixing quantity, which is determined by titration with several different positive sera.

The crude alcoholic extract of beef heart usually was diluted 1:20 and the cholesterinized extract 1:30. In the case of the crude alcoholic antigen the dilution is made by adding 19 c.c. of salt solution slowly with constant agitation to 1 c.c. of the antigen in a bottle previously rinsed in salt solution. This is in order that a turbid emulsion may be produced which is usually difficult in the case of the crude alcoholic antigen unless the salt solution is added very slowly. The cholesterinized antigen is diluted much more rapidly.

The antishoop hemolytic system was used throughout the series. Fresh, not more than 48 hours old, guinea pig serum ordinarily a mixture of serum from three pigs was used in a dilution of 1:10. The quantities of complement and sheep cells were kept constant, 0.1 c.c. of 5 per cent suspension of washed and packed sheep cells being used throughout and 0.1 c.c. of 10 per cent complement. The dilution of the amboceptor is varied according to titration, 2 units

being usually used so long as this dilution hemolyzes completely, when sensitized cells are tested in combination with antigen, in 5 to 10 minutes. A unit is the lowest dilution of amboceptor .05 c.c. of which in combination with 0.1 c.c. of 1:10 complement will completely hemolyze 0.1 c.c. of 5 per cent cells at the end of an hour in a water-bath at 37.5° C.

Tests are set up with 0.02 and 0.01 c.c. of patient's serum with serum controls 0.02 and 0.04 c.c. The total volume is 0.5 c.c., one-tenth the volume of the classical Wassermann test. Serum, antigen and complement are incubated for 4 hours at ice box temperature in the case of the crude alcoholic antigen and for 1 hour in the incubator at 37.5° C. in the case of the cholesterinized antigen. At the conclusion of the incubation period sensitized cells are added and the whole placed in the water-bath until hemolysis of the positive serum and antigen controls is complete, no test being read until its serum controls are completely hemolyzed as well.

#### CLASSIFICATION OF RESULTS

As already stated the study of results embraces 5927 specimens. These have been grouped into two classes, (a) where the two antigens gave like results and (b) where the two antigens gave different results.

TABLE I  
THE TWO ANTIGENS GAVE LIKE RESULTS

		NUMBER	PER CENT
Negative	both	4111	69.5
Positive	both	830	14.0
Doubtful	both	144	2.5
Total		5085	86.0

Table I shows that 5085 or 86 per cent of the specimens agreed in results with the two antigens. Of this number 4111 or 69.5 per cent gave a negative result, 830 or 14 per cent gave a positive result, and 144 or 2.5 per cent gave a doubtful result.

TABLE II  
THE TWO ANTIGENS GAVE DIFFERENT RESULTS

CRUDE ALCOHOLIC	CHOLESTERIN	NUMBER	PER CENT
Negative	Doubtful	479	8.0
Negative	Positive	107	1.8
Doubtful	Positive	153	2.5
Doubtful	Negative	46	0.7
Positive	Negative	9	0.1
Positive	Doubtful	48	0.8
Total		842	14.0



Table II shows that 842 or 14 per cent of 5927 specimens gave different results with the two antigens. Of the 14 per cent giving different results 479 or 8 per cent are in the subdivision which were negative with crude alcoholic antigen and doubtful with cholesterinized antigen. These results are considered to have significance only in cases which have a clinical history or as an indication for further treatment in treated cases. Hence the specimens of this group which are of real interest are the remaining 6 per cent, representing 363 specimens. These have been analyzed as closely as the available information warranted to determine if it was possible on the basis of clinical histories to account for the discrepancies in results with the two antigens.

TABLE III  
CORRELATION OF RESULTS OF 363 SPECIMENS WITH CASE HISTORIES

CRUDE ALCOHOLIC	CHOLESTERIN	HISTORY OF TREATMENT OR POSITIVE	NO HISTORY	INDEFINITE HISTORY	TOTAL
Negative	Positive	38	55	14	107
Doubtful	Positive	77	60	16	153
Doubtful	Negative	19	23	4	46
Positive	Negative	4	4	1	9
Positive	Doubtful	23	20	5	48
Total		161	162	40	363

Table III shows that 161 of 363 specimens gave a clear history of infection, of antisyphilitic treatment, or of at least one previous positive test. In 162 cases either the physician could obtain no history of infection or he failed to transmit his information to the laboratory. Some of these were inmates of the public institutions of the state. In 40 instances the history was indefinite. This included the cases where there had been contact with a recognized case or where there were suspicious lesions but not sufficient evidence for a definite diagnosis. Undoubtedly many of the specimens included in the last two groups could have been placed in the first group if valuable histories had been available.

TABLE IV  
NUMBERS AND PERCENTAGES OF POSITIVE, NEGATIVE AND DOUBTFUL REACTIONS  
WITH EACH ANTIGEN

	NUMBER		PER CENT	
	Crude Alcoholic	Cholesterin	Crude Alcoholic	Cholesterin
Positive	887	1090	15	18.5
Negative	4697	4166	79	70
Doubtful	343	671	6	11

## DISCUSSION

Table IV gives the numbers of tests positive, negative and doubtful with each antigen. It shows that the cholesterinized antigen detects a higher percentage of positive and doubtful reactions than the crude alcoholic antigen. This is accounted for by the greater sensitiveness of an antigen reinforced with cholesterin, a fact well recognized by workers in serology. Because of its greater sensitiveness it is of value in detecting weak reactions which are negative with the crude alcoholic antigen. It must also be remembered that the cholesterinized antigen gives a certain number of nonspecific reactions, hence a result with cholesterinized antigen should never be made the basis of a diagnosis unless supported by history or clinical evidence. However, our experience seems to indicate that a positive result with cholesterinized antigen should be disregarded only after all evidence of its possible specificity has been carefully ruled out.

It was the original intention of the writer to analyze all cases carefully with the aim of dividing them into groups on the basis of age, sex, stage of the disease if present, and history of antisypilitic treatment, or the absence of specific treatment. For some months an attempt was made to induce the physicians to supply fairly complete data. While many of the physicians were extremely courteous

TABLE V  
CLASSIFICATION OF FIRST 1458 CASES OF THE SERIES ACCORDING TO SEX  
AND HISTORY OF TREATMENT

CRUDE ALCOHOLIC	CHOLESTERIN	CASES	TREATED	UNTREATED	MALES	MALES TREATED	MALES UNTREATED	FEMALES	FEMALES TREATED	FEMALES UNTREATED
Negative	Negative	846	87	346	377	60	171	330	26	175
Positive	Positive	291	100	76	146	67	43	87	23	32
Doubtful	Doubtful	46	14	8	17	9	4	12	4	4
Negative	Doubtful	160	26	51	43	15	14	62	11	37
Negative	Positive	41	12	26	15	6	4	21	6	10
Doubtful	Positive	41	19	12	19	10	7	17	9	5
Doubtful	Negative	14	6	1	9	6	1	2		
Positive	Negative	4	1			1				
Positive	Doubtful	15	9	3	10	7	2	3	2	1
Total		1458	274	523	636	181	246	534	81	264

in their endeavors to co-operate, much difficulty was experienced in trying to carry out this plan. In Table V the first 1458 cases of the series have been grouped according to sex and history of treatment or lack of specific treatment. The table illustrates strikingly the difficulty of obtaining data upon which accurate conclusions can be based. It was possible to determine in only 797 of 1458 cases, whether or not antisyphilitic treatment had been instituted. The attempt to classify patients according to age or stage of the disease was abandoned entirely.

#### CONCLUSIONS

1. Two antigens whose reliability has been established form a valuable check upon one another for routine public health laboratory work.

2. Cholesterinized antigen gave a higher percentage of positive and doubtful reactions. This bears out the usual observation that cholesterinized antigens are more sensitive than crude alcoholic antigens.

3. Sera are occasionally found which are undoubtedly positive but which, due to some peculiarity of the serum, do not react with one of the antigens used.

4. Used alone the cholesterinized antigen must be considered a rather unreliable antigen likely to give false positives. Used in connection with the crude alcoholic antigen it is of great value in detecting slight reactions in treated cases where further treatment is indicated or where at least further observation to determine an increase in antibody content in the serum is desirable. It is also of value in picking up slight reactions early in the course of the disease which will later undoubtedly become positive with a less sensitive antigen.



## LUETIN

BY HERBERT C. WARD, M. S., DETROIT, MICH.

*From the Medical Research Laboratories, Parke, Davis & Co.*

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THE need of selecting efficient laboratory aids in the diagnosis of syphilis continues to grow. The complement-fixation test, and the gold chloride together with the allergic test have been submitted for further judgment. The following study aims to help in the selection of such tests or combinations.

In seeking to apply the principles of cutaneous anaphylaxis by using an extract of a syphilitic tissue upon syphilitics, various substances have been employed. Syphilin, an extract made from congenital liver, and palladin, a suspension made from heavily infested lung tissue, were tested with suggestive but discordant results. Luetin, a suspension of killed *Treponema pallida* was produced by Noguchi<sup>1</sup> in 1911 with such encouraging results that it attracted immediate attention.

Noguchi's first 400 luetin tests demonstrated that normal persons gave little or no reaction, that nonsyphilitics otherwise infected gave no reaction, and that in syphilitics this skin test gave results which appeared to be definitely related to the degree of the infection. He described reactive stages progressive in character and ranging from small macules and indurated papules to pronounced pustules with crusting and defervescence. Not only the age of the infection, but the accelerative influence of antisyphilitic medication was considered important. In comparison with the Wassermann the luetin reaction was found later in the early stages and remained less influenced by antisyphilitic treatment. The Wassermann reaction would often be negative while the luetin continued positive. The idea that the luetin test might be safely substituted for the other was clearly discouraged, although some papers published since then have failed to acknowledge this point.

Wolfsohn<sup>2</sup> reported results in 150 cases, particularly of the tertiary, latent, and parasyphilitic groups together with a number of non-

syphilitic infections. He concluded that the luetin reaction was specific for syphilis and successful in the latent stages when the Wassermann frequently failed. In his 23 patients, diagnosed as latent, the luetin test gave 100 per cent positive reactions but the Wassermann only 35 per cent.

Ziegel<sup>3</sup> reviewing the value of luetin, reported the agreement of results by Cohen and Noguchi. Cohen made the luetin test in 60 cases of interstitial keratitis and found a positive reaction agreeing with 76 per cent of the Wassermann and positive in many negative Wassermann cases. He considered that when the infection was modified by treatment the Wassermann became negative while the luetin remained or became positive. If the treatment effected a cure both became negative.

Rytina<sup>4</sup> in 117 cases found the luetin test nearly 100 per cent successful in the congenital, latent, and tertiary groups. He concluded that it was specific and possessed more prognostic significance than did the Wassermann test especially in determining when a syphilitic case might be thought of as cured. In his opinion considerable experience was necessary to correctly interpret mildly positive reactions.

Foster<sup>5</sup> after observing the reactions on 75 cases likewise came to the same conclusions. Stating that the Wassermann test is beset with limitations, suggesting that the luetin may likewise not prove infallible, he nevertheless proposes the combination of both Wassermann and luetin tests as a rational measure of the value of treatment. According to his definition the positive Wassermann reaction is dependent upon recently eliminated metabolic products of the spirochetes, while a positive luetin is dependent upon the absorption of their endotoxines.

The above brief review comprises what might be thought of conveniently as the first chapter in the study of the application of the luetin test. The immediately succeeding paragraphs are concerned with its control.

Some four years following the original presentation of luetin, Sherrick<sup>6</sup> working with a series of 225 cases including a large number of controls reported that potassium iodide given before, simultaneously, or following the injection of the luetin, was provocative of a reaction varying in degree and intensity with the case, but indistinguishable from the previously described classical luetin reactions and developing irrespective of the presence of syphilitic infection.

Kolmer and others<sup>7</sup> verified the findings of Sherrick both in regard to the action of potassium iodide and also of the agar control. They reported luetin-like reactions as occurring as late as one month after the injection of large doses. They concluded, therefore, that a positive luetin has no diagnostic value in cases which have taken potassium iodide. Physicians must rule out therefore every possibility of their patients having had iodide before using the luetin test.

In 1917 Stokes<sup>8</sup> reported the tendency for luetin tested patients to develop positive reactions with agar preparations. He had also noted in previous reports that the old control luetin test occasionally gave a rather high percentage of positive returns. Using oil as a control, Stokes injected both syphilitics and nonsyphilitics with agar suspensions. The results showed typical reactions that were negative in normal and nonsyphilitics and positive in syphilitics. The appearance of the reaction was very similar to luetin. Pustulation usually occurred after five to twelve days and the pustules were slightly more hemorrhagic. He eliminated all likelihood of iodide reactions. In one series of 12 syphilitic cases 10 gave positives, while a second group of 35 gave 15 positives. From his work he concluded that the cutaneous reaction to both luetin and agar is nonspecific in character *but is diagnostic for syphilis*.

In spite of the criticism suggested by these studies, the need for an auxiliary to the Wassermann test continues. In 1916 De Buys and Lanford<sup>9</sup> conducted a comparative study of the tests as applied to congenital syphilitics. According to their findings the Wassermann tests frequently gave negative results as compared with the positive luetin reactions. They concluded therefore that the luetin is much more reliable as a diagnostic guide in this condition than is the Wassermann. Emphasis was made that the luetin test could not be substituted for the Wassermann but that each served a related and a specific purpose, the Wassermann indicating active infection and the luetin inactive. Out of 80 cases, they reported 96 per cent positive findings. One of the most interesting notes was their practice of using a positive luetin upon children as a guide to the discovery of latent syphilis in one or both parents. They emphasized the point that the application of the luetin test especially with young children was far more desirable than the drawing of blood for the serologic. Iodides were carefully eliminated. Positive luetin reactions occasionally developed after two weeks or even later.



A more recent record on the use of luetin is that of Meyers<sup>10</sup> who made trial of it in an outpatient department in San Francisco. In 168 cases he found the luetin test was more reliable than the Wassermann. The collection of reliable data in an outpatient department or in a public clinic is beset with a great many difficulties which interfere with accurate returns. He found that routine luetin tests were extremely valuable and were corroborated by further clinical study.

The present report includes preliminary notes on the value of the luetin test. The work was conducted at the Detroit Board of Health Venereal Clinic for men. Patients are admitted here by personal registration and by reference. The majority present fairly satisfactory histories.

The first series of cases selected for the tests represented a group reported as being serologically positive on first admission. Each case was given a luetin together with a control injection and reactions were noted at two to three day intervals for ten days or longer.

The luetin itself was made according to the original formula except that six strains of *Treponema pallida* instead of two were employed and at least one third of the cultures were older than those which Noguchi used. Luetin from three different lots was employed.

The control luetin material consisted of the combined menstrum of uninoculated *pallida* culture medium tubes, manufactured and maintained under the same conditions as the growing *pallida* cultures.

Injection of the luetin was made as uniformly intracutaneous as possible. Injection blebs measured 5 to 6 mm. in diameter. To obtain ideal injections in varying skin textures and in nervous subjects gave some difficulty at first. It was noticed, however, that faulty or deep injections did not prevent but rather tended to delay typical reactions.

In the second series of patients the test was made upon every case subjected to a Wassermann test. The reactions were read on the seventh day. This record was felt to be safe and of practical convenience to the overworked clinical staff. The results of the two tests were comparable therefore at the same time.

The reactions were of the standard type, a few cases of telangiectasis appeared, and a fair proportion of torpid reactions. One had the impression that patients undergoing intensive treatment showed

mildly indurated elevations residual for a few days and frequently without any typical erythematous phase. This suggested the aborted reaction and proved difficult to estimate. In a few of the pronounced cases the residual pits were easily recognizable a month after their climax.

The complement-fixation tests were made with both the alcoholic human heart and cholesterinized antigens and the technical work was done by the city serologist.

A large number of the sera were run in duplicate in another laboratory. In a series of more than a hundred checks the results ran so closely parallel that the duplication studies were discontinued.

In Table I we have a group intentionally selected to return high per cent positive luetin records together with three normal controls. Assuming the positive clinical history as the standard method of diagnosis it can be readily seen that both the complement-fixation test and the luetin have given very concordant results. One of these tests agreed with every case clinically positive and both tests agree with 23 or 87 per cent of the 26 clinical positives.

By clinical diagnosis therefore there were 26 out of 39 cases syphilitic or 66 per cent. By the Wassermann and also by the luetin test there were 34 out of 39 cases or 87 per cent.

Again by clinical diagnosis there were 13 negative cases, but of these the Wassermann test reported 11 as positive (and of these 8 cases were luetin positive) while the luetin test picked up the two final cases which had been reported clinically and serologically negative.

It is suggestive therefore that in this class of likely syphilitic patients the Wassermann test verifies the clinical findings and increases the discovery of positive cases. The luetin reaction not only supports the Wassermann records in 90 per cent of cases but attracts attention to an appreciable number which have escaped both the clinical studies and the serologic returns as usually made.

With the above findings in mind a group of patients was selected upon which the luetin test might be made in order to ascertain any selective values upon a large mixed and unknown class of potential syphilitics.

Over 400 patients are represented in this series. The irregularity of attendance during the weeks when the observations were in progress was unusually great, on account of the shifting of labor forces and

TABLE I  
RECORD OF THE FIRST GROUP OF CASES

CLINICAL HISTORY		COMPLEMENT FIXATIONS	LUETIN REACTIONS		
Syphilis Latent ==+		Simultaneous with the Luetin test	Pustular ==++ Papular ==+ Negative ==- 5 days 10 days 15 days		
1	-	+	-	-	-
2	-	-	-	-	-
3	-	-	-	+	
4	+	+		+	
5	+	+	+	++	
6	+	+		+	
7	+	+	+		
8	+	+	+		
9	+	+	++	++	
10	+	+	+	+	
11	-	+	-	+	+
12	-	+		++	
13	+	+		+	
14	-	+		+	
15	-	+	+	+	
16	-	-	+	++	
17	+	+	-	-	+
18	+	+	-	+	
19	+	+		-	
20	+	+	+	+	
21	-	+	-	+	
22	-	+		+	
23	-	+	-		+
24	-	+		-	
25	+	+	-	+	++
26	-	-	-	-	
27	-	+		-	
28	+		-	++	
29	+	+	-	-	
30	+	+	+	++	++
31	+	+	-	+	++
32	+	+	+	++	
33	+		-	+	++
34	+	+	+		
35	+	+	+	++	++
36	+	-	-	++	
37	+	+	+		
38	-	-	-	-	
39	+	+	+	++	
40	-	+	+		
41	+	+	++	++	
42	+	+	+	+	
Totals					
Positives 26		34		34	
Negative 13		5		5	



the erratics of the floating population. Out of the total number subjected some 200 were found to have a sufficiently complete set of records to justify their admittance to the final protocol estimates.

The 206 cases are classified in Table II.

TABLE II  
INCLUDING THE TOTAL RECORDS IN THE CLINIC GROUP OF CASES

STUDY GROUP	NO. OF CASES	CLINICAL FINDINGS	WASSER-MANN	LUETIN	PERCENT-AGE	NOTES
Primary	56	Syphilis	+	+	21%	Typical Lesion
			-	+	6%	
			+	-	32%	
			-	-	41%	
Secondary	12	Syphilis	+	+	16 2/3%	Exanthem- atous Stage
			-	+	16 2/3%	
			+	-	50	
			-	-	16 2/3%	
Latent	73	Syphilis	+	+	65%	Obscure symptoms
			-	+	3%	
			+	-	20%	
			-	-	12	
Specials	20	In question	+	+	25%	Records im- perfect
			-	+	25%	
			+	-	35%	
			-	-	15	
Controls	45	Not syphilis	+	+	2%	Normal cases and Nonsyph- ilitic infec- tions.
			-	+	6%	
			+	-	0	
			-	-	92%	
Total No. cases		206				

#### DISCUSSION

*Primary.*—The above divisions have been made with a view to classifying the entire group of cases.

Those placed in the primary group presented themselves at the clinic with the stigmata of beginning syphilis. In several instances dark-field diagnosis established at once the identity of the open lesions. The record of available history, together with the confession of recent exposure and the characteristic ulcers identified this group.

By clinical diagnosis the 56 cases were considered, therefore, to be syphilitic. The returns from the Wassermann records indicated that 53 per cent were positive and the luetin agreed in 40 per cent.

The total luetin positives returned included 27 per cent of the primary group and the luetin positives unsupported by the Wassermann amount to 6 per cent. The total records of agreement of the tests amounted to 62 per cent.

*Secondary.*—The few cases here included limit discussion of this group. All the suspects presented the exanthematous picture together with consistent clinical history.

Of the 12 cases 66 per cent were returned positive by the Wassermann test and the luetin test agreed with 50 per cent of these. The total luetin returns gave 50 per cent positive and the luetin positives unsupported by the Wassermann amount to  $16\frac{2}{3}$  per cent. Total agreements both positive and negative constituted 50 per cent.

*Latent.*—The larger number of patients presenting themselves at the clinic have been exposed to infection over a very indefinite period of time. Vague records frequently report the individual case to have been infected from one to thirty years. He may have had either no treatment, or been subject to intensive. This has been during a few weeks or irregularly during the years. Mindful of his history or forgetful of it, every ill that man is heir to spells venereal infection. Sometimes he is right. Frequently he is in error. However, the clinician has to take the case as it is and establish an independent up-to-date infection status.

Latent cases included, therefore, a group of individuals with obscure symptoms on the day of admission, cases with fair or inaccurate histories of infection, and those who have in the course of their wanderings run the gamut of complete and incomplete antisypilitic treatment.

The Wassermann tests returned 85 per cent of this group as positive and the luetin agreed with 76 per cent of these. The total luetin positive return was 65 per cent of the group and the independent luetin returns 12 per cent. The total record of agreement of the two tests amounted to 79 per cent of the group.

*Specials.*—This class constitutes a list of some 20 cases which could not be diagnosed as frankly latent so as to be included in the preceding class. Many of the records were very obscure and some of the cases permitted only limited observations.

Wassermann tests returned 60 per cent of this series as positive. The luetin agreed with 40 per cent and gave 50 per cent returns on

the entire number. Independent returns by the luetin test amounted to 25 per cent. Total agreements by both tests were 50 per cent.

*The Control Group.*—This division included not only a number of normally healthy individuals but also gonorrheal, chancroidal, rheumatic and tuberculous, together with a number suffering from various skin troubles.

Clinical records gave negative returns. Serologic tests gave 2 per cent positive; and luetin tests showed 6 per cent, and that independently. Both tests agreed in 94 per cent of the 45 cases comprising this group. As a whole the luetin test verified the serologic tests in from 40 to 50 per cent in positive groups and from 40 to 90 per cent in negative groups.

As a supplemental diagnostic it gave from 25 to 50 per cent returns.

As an independent diagnostic aid it gave from 3 to 25 per cent returns.

In reviewing these points it is only right to consider that in applying a test of this kind upon an unassorted group of unknown cases we are measuring its practical rather than its scientific application. The value of the application of the luetin test has as a rule been determined by the returns from the Wassermann. Comparatively little advance has been made during the last ten years in the formula for the luetin while in contrast the Wassermann test has been continually improved. Noguchi, as well as other observers, gave expression to this need of developing the luetin test.

In making comparisons, therefore, one must bear in mind that the contrasting of an improved with an old method can yield findings which appear unfavorable to the use of the luetin test. That this depreciation is only apparent rather than true will appear later.

In a series of 88 cases upon which the luetin test was made, together with a simultaneous Wassermann, the use of alcoholic and cholesterinized antigens abundantly supported the anticipated results.

The luetin reaction was found positive in some 24 cases in which the alcoholic antigen returned negative records while in striking contrast it was positive in only 6 cases in which the cholesterinized antigen obtained negative results.

The relative standing of these two antigens is directly related to the present status of the luetin reaction and this point has not received any special mention. In the present reports the Wassermann reaction was based upon the use of the cholesterinized antigen.



When we compared the luetin and the Wassermann tests upon a series of cases which have been subjected to varying degrees of anti-syphilitic treatment there appeared interesting and valuable suggestions. In Table III are indicated the records on 65 available cases.

TABLE III  
LUETIN REACTION VALUES ON TREATED SYPHILITICS

GROUP	NO.	WASSER- MANN	LUETIN	PER CENT	NOTES
No. 1 Under intensive treatment	25 cases	+	+	28	
		-	+	20	
		+	-	8	
		-	-	44	= Cured?
Totals—Wass. returned negative				64	
Luetin “ “				52	
No. 2 Under moderate treatment	40 cases	+	+	25	
		-	+	30	
		+	-	15	
		-	-	30	= Cured?
Totals—Wass. returned negative				64	
Luetin “ “				45	

In Table III arbitrary division was made into two groups. Individuals of the first had received an average antisyphilitic treatment amounting to 15 salvarsan and 50 mercurial injections. Those of the second series had received an average of 5 salvarsan and 7 mercurial injections. Treatments had been administered within an average period of 18 months and included all available records whether given here or in other clinics.

As indicated both series practically agree, particularly in regard to their negative returns. There is an average return of 25 per cent positive luetins in the presence of negative Wassermann records. Negative returns averaged 35 per cent of the 65 cases and negative returns here should have supremely important values.

The luetin findings are suggestive that the allergic condition continues after the blood is negative serologically. Additional study is greatly needed in order to decide whether the checking of the allergic condition may not be a better method for establishing the probability of curative progress than is the reading of the complement fixation values.

Interpretation of Table III shows that out of a hundred syphilitics under treatment fifteen individuals had been “cured” according to the modern Wassermann test, but not when subjected to the luetin.

That the luetin reaction does actually become negative under the attack of antisyphilitic treatment is apparent from our study. The luetin reaction is proposed therefore as a better indicator of the nearly complete elimination of spirochetes and their products from the human body than any other known test.

The future of the luetin test cannot be predicted. Present indications are reasonably clear that the allergic reaction is negative in normal individuals, in nonsyphilitic infections, and in a certain percentage of treated syphilitics. Since in only a small percentage can the exact degree of infection be definitely established it would appear to be a more practical course to apply this allergic test than to gauge this condition by clinical interview.

Additional study is of serious importance before judgment should be rendered against this thought. The luetin test with all its faults is really representative of a less constantly varying factor of major degree infection than is the complement fixation. Studies upon this problem are now in contemplation.

Criticism of the use of luetin has never been very well supported and much of this criticism is due to the fact that it has not been studied as intensively or as carefully as it should be. The influence of iodides, the pseudoreactions, and our unstandardized formulas have only hindered its recognition. The question of its specificity does not interfere with its application any more practically than does the same question vitiate the use of the Wassermann test.

Criticism of the luetin test has rested frequently upon the findings obtained from relatively too few cases in a given series. Attempts to substitute the luetin test for the Wassermann indicate but an academic attack upon an important problem. Likewise to record, "thumbs down," every time the luetin failed to agree with the Wassermann, reveals nothing but a limited comprehension of this phenomenon.

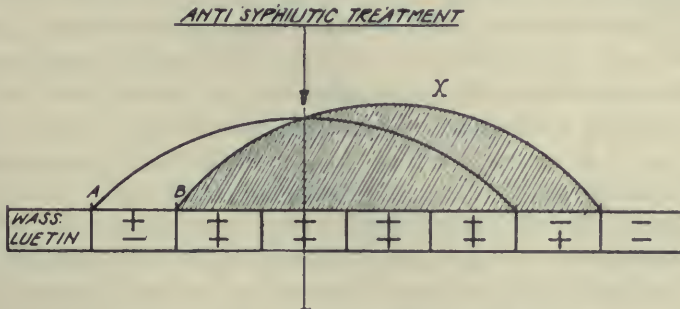
In view of the radically different character of the two tests it is apparent that they are dependent upon quite different factors. These factors, or, prereactional processes, do not rise simultaneously but rather successively. This has been abundantly shown by innumerable tests in the hands of experienced observers. Briefly we have a spirochetosis before we have a Wassermann positive, and we have a Wassermann positive before a positive allergic reaction.

For the purpose of discussion, the following illustration is offered, not as a conclusion to the present paper, or as the summation of statistical figures but as a help to the expression of a group of ideas

in possible explanation of many of the reported findings in the practical use of luetin.

On the basis of suggestions, already published by Noguchi and others, that the complement-fixation reaction is dependent upon the presence of metabolic products of living cells, and that the luetin reaction is due to the accumulation of particular derivatives from the dead spirochetes, the indicated curves are drawn to represent the theoretical changes taking place during the ideal course of a rising and falling syphilitic infection. At about the climax of the complement-fixation curve assumption is made that the patient undergoes

CHART I  
ILLUSTRATIVE OF THE THEORETICAL RELATIONS OF THE TWO REACTIONS



Let curve A represent complement-fixation factors.  
Let curve B represent allergic reaction factors.  
Let sign X represent period of antisyphilitic treatment.

Therefore the following combinations would indicate the stage of infection:

1st stage—	Wass.	-	}	= Primary infection
	L.	-		
2nd stage—	Wass.	+	}	= General spirochetosis
	L.	-		
3rd stage—	Wass.	+	}	= Condition of allergy
	L.	+		
4th stage—	Wass.	-	}	= Progressive control
	L.	+		
5th stage—	Wass.	-	}	= Probational cure
	L.	-		

a period of antisyphilitic treatment (X) changing at once the ratios of the two curves. The amount of treatment is for the present immaterial.

Glancing at the chart one will see the suggestions relative to the relationship of the two reactions. The complement fixation curve is dependent upon infection, and precedes the allergic. This tends to



produce a strong fixation and weak allergic, to a condition of both reactions strong. Antisymphilitic treatment reverses the picture, the complement fixation grows less while the allergic increases until in period No. 7 the complement reaction is negative and the allergic positive. Eventually the allergic became negative and therefore both.

If a group of unknown patients were classified according to the clinical findings of their obscure histories, without other knowledge of the degree of existent infection and subjected to the luetin test, this result would stand illustrative only of the *laws of chance*. And if we were to select most carefully individuals representative of any one identical stage of infection, the resulting records of test would be proportional to the skill of that selection.

Therefore, the efficient value of the luetin reaction as reported by any observer could not be measured by any percentage ratios between it and the Wassermann records. Heretofore scientific effort has aimed to find that the luetin agree 100 per cent with the serologic test. The luetin ratios have measured our ability to choose identical stages of infection and they have indicated the progress of infection and control, but we have failed to interpret.

To employ the Wassermann test only, compels a call for repeated Wassermann tests in the all-important period of early infection. And even when treatment is finished, uncertainty still predominates.

On the other hand the reading of the allergic reaction as here illustrated indicates just where and why it can never replace the complement-fixation test. Its value is limited in the initial stages, but corroborative in the advanced course. At the end of the infection as an independent diagnostic it becomes *immensely valuable both positively and negatively*.

But when these tests are used simultaneously upon this individual they appear to be capable not only of automatically reenforcing each as diagnostic aids but of suggesting more definitely the exact infection stage.

#### SUMMARY

The present report calls attention to the finding of 87 per cent positive luetin reactions in 42 syphilitics. In a second series of 200 unselected cases attending the public clinic there were 75 per cent corroborative returns.

As an indicator of the value of antisymphilitic treatment it has veri-

fied the Wassermann test in a high proportion of cases but remained positive in 10 to 15 per cent.

These findings are suggestive that luetin as a measure of the allergic reaction in syphilis has a much higher value both negatively and positively than has been emphasized heretofore. An explanation of the relationship of the allergic findings and the serologic findings has been presented in Chart I.

Criticism of both the luetin test and reaction has been due to a lack of study and experience rather than from skill in estimating values. Luetin itself is in need of standardization and could be easily improved.

The findings and the opinions recorded here are clearly in harmony with the original report and the more recent literature.

In view of these facts it is believed therefore that the complement fixation and the luetin test should be made simultaneously in every suspected case of syphilis.

Alone each expresses but a limited truth; together a more rational conception is possible, and this is seriously suggestive in the supremely important question, "Is the case cured?"

In acknowledgment of the help received, I take pleasure in expressing my appreciation of the hearty co-operation of the executive and technical staffs of the Detroit Board of Health.

With critical opinion and unusual freedom for work, I have been assisted most generously by Dr. R. S. Dixon, Director of the Division of Venereal Clinics.

For painstaking review and valuable suggestions, I am particularly indebted to Dr. F. W. Baeslack.

Thanks are also due to Mr. E. J. Lindsay for his technical care of the Wassermann reactions.

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## A VALUABLE METHOD OF TREATMENT IN SELECTED CASES OF SYPHILIS

BY W. H. GUY, M.D., PITTSBURGH, PA.

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SYPHILIS should not be treated by rule of thumb. Generalization will lead to disaster. One must treat a patient as well as a disease. Certain cases will not tolerate intensive treatment, and there are those in which a more conservative therapy is not effective. Treatment should be individualized, at the same time holding as closely as possible to certain fundamental principles. Treatment must be long continued—on that point every one is agreed—the only exception being in early primary cases where one may abort the infection by intensive therapy. The fact that nearly all syphilographers treat primary syphilis intensively strengthens my personal opinion that this should be the method of choice, regardless of the stage of the disease, provided the patient is physically fit. We are dealing with a constitutional infection in which a cure is obtained only when every spirochete has been destroyed. In late syphilis inaccessibility of the organism, either in tissues with poor circulation or in masses of comparatively avascular granulomatous infiltration, makes a therapeutic victory more difficult. With iodides to act as resolvents of infiltrations it seems logical to believe, as pointed out by Pollitzer, advocating administration of arsphenamine daily for three days instead of less frequent injections, that the hidden spirochete will much more likely receive a lethal dose of arsenic if the blood stream is kept continuously saturated with the drug as long as is compatible with safety. That the method is not particularly dangerous is attested by the fact that many hundreds of injections have been given successfully in this way. The plan is based on the idea that arsphenamine acts as a direct spirocheticide; if such is the case, the method is sound: if the drug acts indirectly as a tonic, gradually building up to overcome the infection, then it is wrong. Pollitzer and those others of us who have used the method have seen a positive Wassermann persisting under less inten-



sive therapy, promptly reversed. Pollitzer gives arsphenamine on each of three successive days, and follows this with a course of mercury after which he institutes a therapeutic rest. In selected cases I have used the following modification with gratifying results. I give .1 gm. arsphenamine for each 30 pounds of body weight on each of 3 successive days. This is repeated after one month, and again after the same interval. In selected primary cases I occasionally give the second three injections of arsphenamine after an interval of two weeks. My patients are also kept saturated with mercury during this same period, either soluble or insoluble salts being used intramuscularly, dosage being estimated according to the tolerance of the individual. Thus, using, for example, the salicylate of mercury, a course would be recorded approximately as follows:

*Male—weight 150 pounds.*

Jan. 1—Arsphenamine, 5 gm.  
 Jan. 2—Arsphenamine, 5 gm.  
 Jan. 3—Arsphenamine, 5 gm.  
 Jan. 6—Hg. Salicylate 1 gr.  
 Jan. 13—Hg. sal. gr. 1  
 Jan. 20—Hg. sal. gr.  $1\frac{1}{4}$   
 Jan. 27—Hg. sal. gr.  $1\frac{1}{4}$   
 Feb. 1—Arsphenamine, 5 gm.  
 Feb. 2           “  
 Feb. 3           “  
 Feb. 6—Hg. sal. gr.  $1\frac{1}{4}$   
 Feb. 13—Hg. sal. gr.  $1\frac{1}{4}$   
 Feb. 20—Hg. sal. gr.  $1\frac{1}{4}$   
 Feb. 27—Hg. sal. gr.  $1\frac{1}{4}$   
 March 3—Arsphenamine, 5 gm.  
 March 4           “  
 March 5           “  
 March 8—Hg. sal. gr.  $1\frac{1}{4}$   
 March 15—Hg. sal. gr.  $1\frac{1}{4}$   
 March 22—Hg. sal. gr.  $1\frac{1}{4}$   
 March 28—Hg. sal. gr. 2

Upon completion of the course a therapeutic rest of approximately eight weeks is given, after which rest the course is repeated except in dark field positive, Wassermann negative cases. In addition to avoiding the development of an arsenic and mercury fast strain of spirochete, one allows time for recuperation from the intensive treatment

and further is able to obtain a serological check just before beginning the next course that more nearly represents the condition of the blood than one obtained while the patient is on active medication. Three such courses are given in the average case, the amount of medication obviously being varied in different individuals. Also it is occasionally necessary even in selected cases to materially modify the plan. Progressive loss of weight, anemia, evidence of renal irritation, etc., are examples of such indications. In a few cases I have used continuous medication, alternating with mercury and arsphenamine, and my rather limited experience with this modification leads me to favor the plan of intermittent therapy. I have now given approaching 500 injections of arsphenamine by this method (daily for 3 days) without serious trouble. It is essential that the technic used shall conform to known standards, and that the patient be a young vigorous adult in first class physical condition.

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# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs, Arkansas.

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WM. H. DEADERICK, M.D., EDITOR

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## Observation of Spirochetes in the Hanging Drop in Dark-Field Illumination.—

F. W. Oelze. *Dermatologische Wochenschrift*, 1920, vol. lxx, p. 1.

In different methods of examination, the thickness of the same type of spirochetes in proportion to their length is not the same, being greater in the dark-field method. However, this fact does not impair the utilization of the dark-field for the diagnosis of syphilis, as the other spirochetes likewise appear proportionately enlarged, and especially because the diagnosis is rendered upon the basis of the extremely characteristic motion of the *Spirocheta pallida*. Dark-field observation requires the spreading of the serum in a very thin layer, so that the movements of the spirochetes may be practically restricted to a single plane. For theoretical reasons, it is sometimes desirable to observe the motion of the *Spirochete pallida* and the *Spirochete refringens*, respectively, in a larger volume of fluid. A suitable apparatus for this purpose is the Zeiss drop-condensor. On observing the *Spirochete pallida*, the peculiar passive character of its motion is very striking. Whereas in ordinary dark-field observation, currents are almost constantly produced in the fluid through the use of micrometric-screw, and so forth, interfering with an estimate of the motion of the spirochetes themselves, the fluid of the hanging drop remains perfectly motionless. In the hanging drop, the *Spirochete pallida* is seen hardly to leave its place, although it is almost always in a peculiar motion suggestive of the oscillations of an elastic double pendulum. Bending movements are not uncommon. In a hanging drop which furnishes especially good pictures, the *pallida* will be seen frequently changing the height and width of its individual spirals. In a general way, the *pallida* appears to be rather helpless in free fluid, much as if its progression naturally occurred in a solid substratum. This assumption is borne out by the fact that the *pallida* is only very scantily represented in the circulating blood, whereas the affected tissues in part fairly teem with spirochetes.

The behavior of the *Spirochete refringens* is altogether different; the organisms undulate actively about in the fluid, rushing to and fro in the thickness of the drop. When the hurrying *Spirochete refringens* encounters a still intact



white blood corpusele, its beak-like extremity seems to penetrate into the leucocyte in an evident effort to liberate itself. The undulating movement is so rapid that the eye is no longer enabled to distinguish the individual convolutions. These extremely hurried movements are never seen in the case of *Spirochete refringens* which creep about within a loose structure of cellular debris or bacterial collections. This seems to indicate that the *Spirochete refringens* cannot move in a solid substratum, but is dependent upon fluid, which may sometimes be filled with cellular debris.

The spirochetes of *ulcus gangrenosum penis* and of *Plant-Vincent's angina* are midway between the *refringens* and the *pallida* in their mode of movements in the hanging drop, rather resembling the *refringens*, however, which is also in conformity with the pathologico-anatomic findings.

**Motion of the *Spirochete Pallida*.**—F. W. Oelze. *Münchener Medizinische Wochenschrift*, 1920, No. 32, p. 921.

The *Spirochete pallida* is differentiated from the nonpathogenic buccal spirochetes, more particularly the *spirochete dentium*, primarily by the character of its motion. By means of a special apparatus, with light and dark-field condensor, as well as other improvements of the original ultramicroscope, the author was enabled to obtain remarkably good pictures of unstained or stained specimens. On investigating the locomotion of the *Spirochete pallida* with this apparatus, it will be found that a distinction must be made between *motion* and *progression*. In fresh quartz-chamber specimens, observed at body-temperature, the *Spirochete pallida* presents the familiar rotatory motion, which can only be recognized as such by careful examination. At first an impression is conveyed of a to and fro swaying of a double elastic pendulum. Evidently, the appearance of the spirals may simulate movements, since they are seen in variable perspective while swaying to and fro. This unanimous swaying of the ends of the *Spirochete pallida* is of importancæ for the diagnosis. Especially in specimens which contain several spirochetes in the visual field, the impression of a certain rhythm is produced, which is characteristic of the *pallida* in contradistinction from the buccal spirochetes. On careful examination, the *pallida* is found to be acutely rotating. The apparent swaying to and fro is explained on the basis of psychologic physiology. The *pallida* rotates, but there exists no perfectly straight specimen, they are all slightly curved. Hence the curved ends describe circles in the rotation and are seen with special distinctness when they appear in the plane of the object-carrier, producing the impression of the spirochete swaying to and fro in this plane. The last convolution of the spirochete often presents an independent, more rapid motion than the remaining portion. It is noteworthy that a spiral is frequently missing, a straight more or less extensive segment appearing in its place. This straight segment may also change its position during the rotation; this goes to show that in spite of the so-called rigidity of the *pallida*, its shape is not immutable. The spirals of the *pallida* are by no means regular, but only appear to be so, because in the customary magnifications they present them-

selves under a smaller visual angle than the other spirochetes. Under a high power, the convolutions of the pallida can be seen to be very irregular, in fresh as well as in Giemsa preparations.

Besides rotation, the pallida has a noteworthy "bent" motion. This bending takes place near the middle, lasting from one-fifth to two-fifths of a second, although the pallida may remain for a long time in this bent attitude. As a rule, it bends towards the side of its slight curvature. The bending does not involve a loss of elasticity of the spiral. As to a progression of the pallida being caused through rotation and bending, the author's accurate measurements of fresh specimens yielded the unexpected result that this is *not* the case. When the Spirochete pallida is freely suspended in the serum, the rotation does not induce any change in position; nor does it advance by bending, although the end of the spirochete may be displaced by 6.8 or 10 micromillimeter after several bendings. The pallida tends to change the position of its axis in space in the hanging drop, from vertical to horizontal; this phenomenon manifests itself also in the quartz-chamber specimens, but has nothing to do with progression. These observations on pure serum specimens indicate that the pallida is practically immovable in fluid media. As it is known to infest the entire human body, the pallida evidently can move better in solid media. Some experiments showed that a mixture of 5 per cent gelatine, diluted with the same amount of serum and added to the undiluted drop of secretion, constitutes a suitable substratum. Preparation and examination of the specimen must take place at body temperature. The pallida is a very sensitive organism as regards its motion, which can be observed only under very favorable conditions. The well-marked rotation of the pallida is active only in a substratum of variable solidity. It is often seen to creep several times rapidly forwards and backwards, in exactly the same direction; the spirochete apparently seeking to penetrate forcibly into a solid substratum. When unsuccessful, it changes its direction very slightly, about 1 micromillimeter, apparently seeking some weaker point for its penetration. Even under the most favorable conditions, these movements last only a few hours.

#### Advantages of Different Methods of Demonstrating the Spirochete Pallida.

F. W. Oelze. Dermatologische Wochenschrift, 1920, No. 42, p. 843.

The improved construction of the dark-field condensers permits the securing of very good views of the Spirochete pallida, optically correct dark-field examination offering various fundamental advantages. In the first place, no other of the customary methods shows the pallida in the living state, with all its delicate movements. The concentration of the serum, namely, the probability of finding spirochetes, is greater with the dark-field method than with any other procedure. Further, the dark-field illumination is uniform throughout the entire extent of the specimen. None of the staining methods furnish such uniform results, good and poor localities being distinguishable in the stained smear of the majority of the cases. In certain areas, the pallida is clearly and distinctly recognizable, whereas in other places, even the structure of



the background indicates the probable absence of spirochetes. It is a peculiarity of all staining methods without exception that they do not uniformly represent the delicate pallida over the entire specimen. It makes no difference for the dark-field representation at which point of its life cycle the pallida has arrived; whereas in the staining or impregnation methods, the temporary state of the organism is of importance. Finally, the demonstration of the pallida in the dark-field is not dependent upon the number of corpuscular elements accidentally contained in the visual field; not so much relatively large bodies, such as leucocytes or red blood corpuscles, but rather small granules and submicrons, which in stained specimens may prevent the pallida from being rendered visible. Dark-field examination shares with the staining methods the disadvantage that spirochetes lying in cellular collections are not represented.

Comparative examinations of a definite serum in the dark-field and by means of stains, yielded very marked differences in regard to the contents in spirochetes. Only the Giemsa stain after osmium fixation showed a considerable number, about two-thirds of the existing spirochetes. All the other methods furnished about one-third; only the India ink method failed greatly, showing less than one-twelfth of the spirochetes. The technic employed in these examinations really favored the stains, as only small drops of especially clear sera were examined.

The life cycle of the *Spirochete pallida* evidently includes certain stages where it still possesses the behavior of its refraction index which permits dark-field observations, but where fine chemical changes already involve an altered behavior towards staining agents. It must be assumed that the *Spirochete pallida* is adapted to staining only up to a certain stage in its individual existence.

**Glaucoma and Syphilis.** Lapersonne. *Le Progrès Medical*, 1920, No. 51, p. 554.

Syphilis is often responsible in a variety of glaucomatous conditions, in the so-called prodromal glaucomas as well as in acute or subacute glaucoma. Congenital syphilis is apparently the causative factor in a certain number of cases of glaucoma where chorioretinal or iridocyclitic lesions accompany the glaucomatous syndrome. Many secondary glaucomas after iridochorioiditis and iridocyclitis are due to syphilis. The changes predominate in the anterior segment of the eye, and the tension is very high, but the papilla rarely becomes excavated. Hydrophthalmia, often accompanied by interstitial keratitis, is frequently referable to syphilis. In all these cases, the specific infection may act either by producing local lesions (iridocyclochorioiditis) or vascular lesions. It may act indirectly, by determining renal lesions, which affect the eye only secondarily, through changes of the blood.

The surgical indications are governed by the existing clinical form, iridectomy being reserved for acute or subacute conditions, and fistulization for chronic cases. These interventions must be combined with general treatment, mercury and arsenobenzol, which has excellent effects upon the subjective disturbances, the hypertension, and the lesions of the anterior segment of the eye.



**An Analysis of Over 500 Cases of Genital Chancre in the Native Male.**—P. H. Hennessy, Kuala Lumpur, India. *Indian Medical Gazette*, 1920, vol. lv, p. 327.

During the investigation of this series, it was interesting to note the large number of cases which had secondary manifestations on the penis. In some an ulcer had appeared on the site of the old scar, in others the area attacked was a fresh one, and in many no scar was discoverable to help the diagnosis of a previous infection. As the series was confined to cases of recent infection, these secondary cases were not included. The occurrence of secondary syphilitic ulceration of the penis is not uncommon and may not be associated with other definite signs of the disease. It is with this type of case that the history of the disease becomes so puzzling. With some Chinese patients a distinction is made by the patient between a sore contracted in China and in this part of the world. The value of intravenous injections of the novarsenobenzol and the other arsenical preparations can hardly be overestimated. In fact, so popular did this form of treatment become that some of the Chinese and Tamil attendants insisted on receiving its advantages. They all admitted early indiscretions and, to make protection doubly secure, some of them produced their wives, who were not to be denied a share in the cure so rapidly secured for rheumatism and pains in the bones. Novarsenobenzol, luargol, and galyl were used; but novarsenobenzol was quite the most adaptable for general routine work. A fair supply of neosalvarsan existed at the time the Great War started, and was most useful till a regular supply of novarsenobenzol was obtained. Although with galyl some rather exciting moments were experienced, the only death that occurred was with the German preparation—neosalvarsan diluted with 300 c.c. distilled water. This case, a woman, had convulsions, intense jaundice, hemorrhage and death on the fifth day. With novarsenobenzol no untoward results were noted except in those patients who did not obey the instructions of not eating before the injection. Vomiting was almost immediate; and a certain amount of collapse and cyanosis was noted in one case, a Japanese female who had a hearty meal a few minutes before the injection. Intramine was tried, but gave rise to so much pain that it became unpopular. The new variety in two solutions is not so painful. (There is no drug so efficacious in the treatment of acute gonorrheal rheumatism as intramine.) It will be remembered that the majority of cases had multiple sores. To what extent a mixed infection exists is not easy to say. That it does occur is undoubted, and with sepsis to disguise the main characteristic an exact diagnosis for some time may be impossible. The Medical Research Committee recommend a period of 12 weeks' repeated observations for syphilis before a diagnosis of "soft sore" is made. The Committee find no sufficient evidence that what is clinically known as a "soft chancre or soft sore" is a specific disease induced by a single species of microorganism. The impossibility of such observations in the native coolie class need only be mentioned. If one's object of complete cure is not attainable in the class of patient mentioned, it is certainly a consolation to know that a large number have been rendered

less infectious and that, for a period at least, a state of health has been arrived at which enabled all of the series to return to their work.

**Paralysis Agitans and Syphilis.**—Bernard Oettinger, Long Beach, Cal. Medical Record, 1920, vol. xeviii, p. 15.

This patient passed from her initial lesion to an acute cerebral syphilis without noticeable or, at least, any persisting cutaneous sign; also the outstanding feature of her complaint for her and her environment was a monoplegic disability pointing to cerebral origin, a fact to which the Argyll-Robertson phenomenon testified as well. After a single intravenous injection, the pupils began to contract and the patient had regained full control of her right leg. With pupillary symptoms of recent origin, vigorous antisyphilitic treatment may right them entirely or in a similar case, the Argyll-Robertson pupil might never be a part of the clinical picture. Such a patient seen at a later period may perhaps complain solely of pain and consequent disability as in cases a, b, and c. With associated lack of characteristic paralysis or involvement of the deep reflexes as in the cases cited, the unblemished skin would mean absence of an important diagnostic clue. The Wassermann reaction may at times assist in establishing the true etiology of chronic pain. But even so, late syphilis often shows a negative blood or spinal fluid reaction.

**Rummoa-Ferranini Genito-Dystrophic Geroderma (Senilism) Lean Type, Due to Tardy Hereditary Syphilis.**—Mariano R. Castex and Carlos P. Waldorp, Buenos Aires, Argentina. Medical Record, 1920, vol. xeviii, p. 1009.

To recapitulate the results of the somatic examination: depression of the posterior fontanel, slight alopecia on the temples, venous network on the forehead, eyebrows thinning toward the end, irregular and eccentric pupils, aniso and microdontism, ogival palate, microadenopathy, splenic tumor, cardiohypertrophy (contributing causes to which are: Hereditary syphilitic infection, smoking habit, and onanism), aortitis and rugose bones. These indicate that the patient is branded with very numerous stigmata of hereditary syphilis, some of which are original stigmata, and not of active hereditary infection, all confirming the synthesis of a dystrophic hereditary infection (syphilitic). Furthermore, there is a series of manifestations on the side of the respiratory organs: the thorax, seen on inspection to be assymmetric, with greater arching of the left hemithorax; chronic bronchial catarrh and emphysema, the origin of which may be attributed to the triple action at work: in this case tobacco, hereditary infection, and tuberculosis. We must not fail to remember the frequent presence of acute and chronic bronchopathies in secondary and tertiary infection, which affords an excellent soil for the bacillus of tuberculosis—the frequent existence of which is proved by the efficacy of iodide of potassium in chronic bronchitis; in the present instance, treatment by mercury and iodide sufficed to banish the bronchial phenomena. But the most interesting group of symptoms is instanced by a condition of pluriglandular dysendocrinia. A slight hypothyreosis represented by soft and well-developed thyroid

enlargement, thinning of the hair in the region of the temples, as well as in the tip of the eyebrows, and dental dystrophy related surely with disorders of ontogenesis, of hereditary syphilitic origin. A slight hypopinephria, marked by: pigmentary cicatrices (which can be produced by means of the caustic test), the positivity of Sergeant's line, arterial hypotension, and the recorded data about easy fatigue, muscular asthenia, etc. Another group of symptoms points to a very pronounced dyspituitarismus, namely, large face (compared with the skull), facial angle very pronounced, occipital prognathism, cervico-dorsal typhosis, large hands and feet, massive, rapid, precocious growth prior to puberty, and enlargement of the sella turcica as shown by radiography. Thus grouped, these elements are typical of acromegalic hyperpituitarism. There remains still another aggregate of symptoms: Scanty growth of hair on the pubis, complete lack in the axillæ, on the trunk, face, lips and chin, and only a few scattered hairs on the legs. The face is singular in appearance: beardless, parchment-like, xerodermic in a very intense degree, thick-lipped mouth, ogival palate, and teeth of the description already given. As to the genitals, there is a small hypoplastic penis, with atrophic testicles and epididymis; the testicles painless to pressure and almost completely sclerosed; to which may be added imperfect erection and problematic ejaculation. These elements all go to show typically a state of hypogenitalism, and a clinically well-defined form of the same—eunuchoidism.

**Pseudochancro of the Lips with Fusospirillary Symbiosis.**—H. Jamin. *Annales de Dermatologie*, 1920, Vol. 1, No. 4.

This observation on a native of Tunis concerned the differential diagnosis between syphilitic chancre and Vincent's angina. The lesions which he presented on his lips were interpreted by two physicians in succession as syphilitic chancres. One was situated on the lower lip, on the right side, in the cutaneous portion; the other involved the left labial commissure and affected especially the mucous portion of the lip, with slight involvement of the skin surface. Both ulcers were of irregular configuration and had very irregular margins; their color was yellowish and suggestive of the borders of soft chancres. The floor of the ulcers was dark red, proliferating, and secreted a large amount of thick pus. There was no pseudomembranous covering, the border was distinctly outlined, yellowish white, surrounded by a bright red congested margin. The entire ulcer rested on an indurated base, which extended beyond the lesion; this induration was yielding on digital pressure, edematous, and inflammatory. This exploration proved very painful. Salivation was rather excessive, and the breath was offensive. The submaxillary glands were swollen and painful. The lesion was of twenty-five days' standing and had begun at the labial commissure in its mucous portion, in the form of a pimple which rapidly increased in size. About the eighth day, the lesion of the lip made its appearance. The patient insisted that he had never had syphilis. Although the lesion quite closely simulated a luetic chancre, the diagnosis was elucidated by laboratory examinations which showed that both ulcers contained an ex-



tremely abundant fusospirillary association. Repeated ultramicroscopic examinations were carried out, as buccal chancres are not infrequently complicated by infection with the bacillus and spirillum in symbiosis, but showed merely the existence of the thick spirillum, with large convolutions and extensive movements. No treponema were demonstrable. The Bordet-Wassermann reaction, made in the Pasteur Institute in Tunis, proved negative. The diagnosis of pseudochancere with Vincent's symbiosis was accordingly rendered and was confirmed by the effects of treatment.

**The Treatment of Syphilis of the Central Nervous System.**—Clyde L. Cummer, Cleveland. *Ohio State Medical Journal*, 1920, vol. xvi, p. 663.

Treatment is at best uncertain. In the most favorable cases it must be intensive and protracted; in some manifestations, it may be utterly powerless. Success depends upon the early institution of treatment. On account of this, prompt recognition of invasion of the central nervous system is vital, so that irreparable damage may be prevented. It is even more important, however, to prevent cerebrospinal sequelæ by treating all syphilitics vigorously and by keeping them under observation until clinical and laboratory examinations prove that the infection has been eradicated in the nervous system as well as elsewhere. On account of the certainty that many syphilitics will inevitably develop cerebrospinal lues in spite of every precaution, it becomes all the more important to lend our aid in fighting this great plague.

**A Valuable Method of Employing Arsphenamine in Syphilis.**—Oliver S. Ormsby, Chicago. *Journal of the American Medical Association*, 1920, vol. lxxv, p. 1.

The method of treatment described in this communication proved efficient in a number of cases resistant to other methods. The absence of untoward results and reactions of any moment in the large number treated makes it appear as safe as other methods. The percentage of cases remaining Wassermann negative and clinically free over a period of from one to three years is not large, as many of the patients, after having two or three negative tests over a period of from six to nine months after the termination of treatment, have not since reported for examination. A comparison with results from other methods cannot be made, owing to lack of extended reports of cases treated by other methods, the major portion only having been watched for less than one year. Several reports are available of cases treated in the chancre stage, and they are similar to ours in end-results. It appears evident from experimental work herein reported that frequently repeated small doses, that is from 0.1 to 0.5 gm. are inefficient. The combined use of arsphenamine and hydrargyrum in periods either as herein described, or by the method commonly employed today in which arsphenamine is administered every five to seven days in periods of five to eight injections, appears at present to be the method of choice. The promptness with which many patients become clinically free and Wassermann negative, often with a single course, is encouraging, but

should not lead to the conclusion that the disease is eradicated, as Wassermann relapses occur from six months to a year or more after having been continuously negative in the interim. It is therefore necessary to continue treatment for from one to two years, even though it may seem superfluous in some cases. The length of time that a Wassermann positive should be treated, and the amount of treatment that should be given, cannot be stated. When a patient is clinically well and has been for years, and has had a large amount of treatment without permanently affecting the blood reaction, it is difficult to say how far we are justified in pushing treatment. In certain of these a spinal fluid examination reveals findings that are significant; in many it does not. Finally, it can safely be stated that with arsphenamin and mercury together we have a method of combating syphilis that is better than any method previously employed; and until more efficient drugs are found these should be used at the earliest possible moment, and continued a sufficient length of time to eradicate the disease, or demonstrate the inability of the drugs to accomplish this result.

**Hypersensitiveness to Arsphenamine Following Exfoliative Dermatitis.**—Harold C. Stuart and Edwin P. Maynard, New York. *Archives of Internal Medicine*, 1920, vol. xxvi, p. 511.

Reactions following arsphenamine or neoarsphenamine therapy may be divided into four types: 1. Nitritoid crisis. 2. Herxheimer reaction. 3. Acute arsenic poisoning. 4. Chronic arsenic poisoning. A case of exfoliative dermatitis or chronic arsenic poisoning is presented. The first cutaneous manifestations were persistent itching, papular eruptions on wrists and shins. It is possible that the irritative meningitis following the preceding treatment may have been the beginning of the symptoms of hypersensitiveness. Cutaneous hypersensitiveness to arsphenamine and neoarsphenamine occurs in patients who have suffered from exfoliative dermatitis. This was demonstrated by typical skin reactions in two such patients by means of intradermal injections of minute dilutions of the drug, but could not be demonstrated in a third, perhaps because the tests were made nine months after the dermatitis when the hypersensitiveness had subsided. This supposition, if substantiated, would make the skin reaction of practical importance in determining when it is safe to renew the arsphenamine treatment.

**Treatment of Syphilis.**—Hilary J. Connor, Providence, R. I. *Rhode Island Medical Journal*, 1920, vol. iii, p. 180.

Out of 37 patients examined five years after treatment, 33 were found negative, or nearly 90 per cent. The 33 negative cases all received three or more intravenous treatments of neosalvarsan .9 gram, and three of these patients were given protiodide and inunctions of mercury. Four of the patients examined were found positive. One primary case received two intravenous treatments of neosalvarsan .9 gram and developed tabes dorsalis. Another primary

case received two intravenous treatments of neosalvarsan .9 gram and developed cerebral syphilis. One secondary case received one injection of salvarsan .6 gram during the first year. The patient is now under treatment with a four plus Wassermann and positive symptoms. Another patient with no diagnosis as to stage, receiving three intravenous treatments of neosalvarsan .9 gram first year, is now under treatment with four plus Wassermann and symptoms.

**The Administration of Arsphenamine by Retention Enema.**—John L. Mandracchia, Brooklyn, N. Y. *Medical Record*, 1920, vol. xcvi, p. 144.

The administration of arsphenamine by retention enema is a successful and practical method of giving this powerful drug and therefore the method demands a place in the therapy of syphilis. The slow absorption is an advantage and prevents the production of nitroid crises. In children it is the method of choice. The contraindications to this method are nil. The results obtained by this method are just as good as those obtained with the intravenous method.

**Sulfarsenol in the Treatment of Syphilis.**—Carminow Doble, London. *Lancet*, 1920, vol. cxcix, p. 243.

Sulfarsenol appears to be equal to any other form of salvarsan or neosalvarsan except as regards speed of disappearance of the Spirochaeta pallidum, at any rate in primary and secondary cases. The hypodermic method of administration is fool proof and practically painless. It seems an ideal method for infants and those with difficult veins. Up to now the author has had no side-effects, not even a slight rise in temperature; the usual contraindications do not appear to be applicable in anything like the same degree as "606" or "914." Intramuscularly it is less painful than "914," and can be given dissolved in distilled water. Intravenously the slightness of the Herxheimer renders less danger in cases with central nervous symptoms.

**Salvarsan-Mercury Intravenously.**—J. Constance Klecan, Portland, Oregon. *Northwest Medicine*, 1920, vol. xix, p. 266.

Mercury can and should be given intravenously, that mode of administration being perfectly painless and safe. The results are prompt, both from symptomatic and serologic point of view. Patient is saved time, money, and his period of mental anguish is decidedly shortened.

**Syphilis at the U. S. Army Base Hospital, Camp Greene, Charlotte, N. C.**—Clyde F. Ross, Richmond, Va., and Walter A. De Foe, Detroit, Mich. *Journal of the Michigan State Medical Society*, 1920, vol. xviii, p. 60.

No one sign, either laboratory or clinical, should be depended upon for the diagnosis of syphilis, but the laboratory and clinical signs should be closely examined and conclusions reached by a study of all the information available, never forgetting that the diagnosis of syphilis was made long before the ad-



vent of the Wassermann. The ideal time to begin treatment in syphilis is before the appearance of the positive Wassermann during the primary stage. This should be our aim in our future relations to the treatment of this disease. Nine per cent of their chancres were multiple while thirteen per cent were of the mixed variety; that is, both chancres and chancroids were present. Primary syphilis can be diagnosed and all active lesions healed in twenty days, with an average administration of three doses of arsphenamine and two injections of mercury. Secondary syphilis can be diagnosed and all active lesions healed in sixteen days, and with two and a half doses of arsphenamine and two injections of mercury. The administration of arsphenamine is not without danger and it should not be administered except when indicated; which indication is the existence of syphilis, active or latent, and then only under the best conditions possible, and by one who can meet any emergency that may arise. The negro is more amenable to treatment than the white man as shown by the comparative length of time spent in the hospital by the two classes of patients

**The Treatment of Tertiary Lues with Dijodyl.**—F. W. Oelze    Dermatologische Wochenschrift, 1920, vol. lxxi, p. 748.

The author in his experiments made use of dijodyl-Riedel, which is a compound of unsaturated oxy-fatty acid with iodine, namely ricin-stearolic acid dijodyl, its formula:  $C_{18}H_{33}O_5J_2$ , with iodine contents of 46.2 per cent. According to its constitution, this substance passes undecomposed through the stomach and is gradually saponified in the bowel. Phenomena on the part of the stomach, otherwise frequent in iodine medication, are therefore excluded with this preparation, in spite of its relatively very high iodine content. Judging from numerous experiments, dijodyl is very readily tolerated; the only side-manifestation was a mild coryza, in a few rare cases. A uniformly good effect was obtained in the treated cases of tertiary lues. An especially instructive case is briefly described as follows:

The patient, a man forty years of age, who denied venereal infection, suffered about fourteen years ago from a sore on the mouth, which healed after about three weeks. Recently, he noticed two hard nodules in the right lower lip and cheek, which caused merely a sensation of tension, until they became ulcerated about three months later. When the patient came under observation in the Dermatological Clinic of the University of Leipsic, the right cheek was found to be swollen and discolored, especially in its lower portion; a tumor the size of an apricot could be palpated in the adjacent buccal angle. The tumor was covered by an ulcer the size of a cherry,  $\frac{1}{2}$  cm. in depth; the margins projected and the floor was covered with a yellowish deposit. Another, smaller ulcer was seen externally and to the right. The mouth could be only imperfectly opened. The cervical glands were not enlarged. Exploratory incision. No fungi. Wassermann reaction, negative. The diagnosis was: disintegrating gumma at the right labial angle. Prescription: Sterile dressings, hygiene of mouth, daily three tablets of dijodyl at 0.3 g. Thirteen days later

the ulcers had become much smaller, and the protruding margin was flattened. Subjective condition was very good, and the patient was discharged with the instruction to take five tablets daily. Three weeks later he was seen again, looking remarkably well, the ulcers had healed, leaving a linear scar; a tumor was no longer palpable. Continuation of the diiodyl treatment was recommended.

The dosage was further diminished later on in similar cases. It was found under steady control of the urine, that on administration of only one diiodyl tablet daily, the patient maintained a uniform excretion of iodine. Chewing of the tablets is a preliminary requirement; if this is objected to, diiodyl may be prescribed in capsules. Failure of absorption could never be demonstrated in the author's experience.

The difference in the quantity of iodine which leads to the same therapeutic effect from potassium iodide and diiodyl is very noteworthy. Under the customary potassium iodide treatment, the patient receives about 80-100 g. potassium iodide monthly, i.e., about 65 g. iodine. Under daily administration of two diiodyl tablets at 0.3 g., which is a sufficient amount, he receives only 18 g. diiodyl, i. e., 8 g. iodine. It follows from the constitution of diiodyl that it is slowly absorbed from the intestinal tract. As shown by statements in the literature, diiodyl with reference to the same amount of iodine as potassium iodide, is excreted during a longer time. This, in the author's opinion, explains the better action of diiodyl and the very inconsiderable side-effects following its use. The improved general condition of the patient is presumably due in part to the cure of the disease. On the other hand, it is also a known fact that iodated and bromated fats pass directly into the body and are deposited. As diiodyl belongs to this class of substances, it is not excluded that an increase of the body weight results also in this way.

**Diagnosis of Spirochetoses.** A Sartory. *La Progrés Médical*, 1920, No. 52, p. 566.

The author's contribution includes a description of several procedures in use for the demonstration of the *Treponema pallidum* in syphilitic lesions, such as chancre, mucous patches, and various other lesions. The surface of the chancre is cleaned by means of a small piece of absorbent cotton. The ulcer is gently touched with a platinum wire or a spatula which has previously been passed through a flame, and a slight exudation is obtained, some investigators prefer the production of oozing by lateral pressure. The technique is similar for mucous patches. The pus is spread out on very clean slides, and these are stained by the methods of Giemsa, Laveran, or Fontana-Tribondeau. After the removal of the exudate, a drop of it may also be placed upon a slide, near a drop of India ink. Mix spread in a thin layer by means of a platinum wire, dry in the air, and examine with the immersion objective. The treponemas appear light on a dark background.

Ultramicroscopic examination shows the living organisms. For this purpose, a drop of pus or serum is placed between slide and cover-slip, and ex-

ained with the ultramicroscope. The treponemas appear bright on the black background, with very regular spirals (eight to fifteen convolutions) and tapering extremities. The spiral turns are very close and regular.

From the viewpoint of the differential diagnosis, it is important not to confuse the *Treponema pallidum* with other spirochetes, such as the *Spirochete refringens*, the *Spirochete dentium*, *buccalis*, *balanitidis*, *gracilis*, *Vincenti*, the spirilla of recurrent fever, etc. The ultramicroscopic examination and examination after staining, already permit the elimination of several of these organisms. For the remainder, the character of the lesion must be taken into consideration, besides the morphologic features of the various spirochetes.

**Discrepancies in the Wassermann Reaction.**—E. H. Ruediger, Bismarck, North Dakota. *Journal-Lancet*, 1920, vol. xl, p. 565.

Glycerolated human serum gave much stronger positive results than did nonglycerolated human serum, in some cases the differences being as great as 16 to 1. Fresh glycerolated human serums frequently fixed complement better when diluted 1:4 or 1:8 with 50 per cent solution of glycerol than when undiluted, but glycerolated human serums about a month old invariably fixed complement better when not diluted, still the total quantitative result usually remained unchanged. Complement serums from different guinea pigs varied greatly in fixability and in hemolytic power. Of a number of complement serums tested with the same human serum some gave 2 plus, some gave 3 plus, some gave 4 plus, some gave 5 plus, some gave 6 plus, some gave 8 plus, and others gave 10 plus. The use of different antigens led to different results. Antigen prepared from dog heart or from guinea pig heart frequently gave false positive results. Alcoholic extract of beef heart frequently gave stronger positive results than did alcoholic extract of human heart, but false positive results have not been obtained with the beef antigen. Alcoholic extract of rabbit heart was about equal to alcoholic extract of human heart, while alcoholic extract of sheep heart was somewhat inferior. The acetone-insoluble antigens of beef heart and of dog heart were greatly inferior to their corresponding plain alcoholic extracts, and acetone-insoluble antigen of dog heart gave false positive results, as well as did the corresponding plain alcoholic extract. Alcoholic extract of human heart muscle diluted 1:50 or 1:100 usually fixed complement better than when diluted 1:25. Alcoholic extract of human heart muscle diluted 1:100 with physiologic salt solution rapidly became anti-complementary; diluted antigen six hours old gave 2 plus with negative serum, and diluted antigen twenty-four hours old gave 10 plus with negative serum. Glycerolated syphilitic serums fixed complement better at low temperature than at high temperature. A serum which gave 1 plus when incubated at 37° C. for one hour gave 4 plus at 10° C. for seventeen hours, 6 plus at 3° C. for seventeen hours, and 10 plus at 1° C. for seventeen hours. A human serum which, without the addition of glycerol, gave a negative result when incubated at 37° C. for one hour, gave 96 plus when glycerolated and incubated at 1° C. for seventeen hours. Another human serum nonglycerolated and incubated at



37° C. for one hour gave 8 plus and when glycerolated and incubated at 1° C. for seventeen hours it gave 2,000 plus. Differences in the technic of performing the Wassermann test lead to great differences in the results, and the only remedy is standardization of the technic.

**Status of the Luetin Test.**—Louis Hannah, Sylvania, Georgia. *Medical Record*, 1920, vol. xcvi, p. 522.

Having seen no reports in the current literature on the records of the luetin test, whereby its standard of efficiency might be established, the author's impression is that, unless the medical world or proper authorities are in accord with the status assigned to the test, it should be eliminated from standard text books—until perfected—as one of the methods for the diagnosis of syphilis. It is far from his purpose to discredit the efforts in this particular investigation of as eminent an authority as Noguchi, but he does consider that the profession should be spared the expense and disappointment of employing a method of diagnosis that is uncertain and misleading. It would be worth while to know what conclusions others have reached in regard to the luetin test.

**The Effect of Mercury Salicylate on the Wassermann Reaction.**—Herman Goodman, New York. *Archives of Dermatology and Syphilology*, 1920, vol. ii, p. 193.

Eighty-seven previously untreated latent syphilitic patients with 4 plus Wassermann reactions were given 1 grain of mercury salicylate intramuscularly at weekly intervals for courses of from six to eight injections. The Wassermann reaction immediately after treatment remained strongly positive in 66 per cent of the cases. In only 9 per cent was there a reversal to negative; and in some such patients who were given a third Wassermann test after an interval without treatment, the reaction was positive. It seems fair to conclude with Nelson and Anderson, who carried on a similar study in 1915, that mercury salicylate alone in the dosage and for the period given does not qualify as a curative agent in syphilis. The plans for a longer study were curtailed by the demobilization. In the future, mercury salicylate will be used in increasing doses up to 2 and 2½ grains weekly in an effort to learn whether mercury salicylate in larger doses is effective.

**A Course of Treatment for Early Syphilis.**—G. O. Scott and G. H. J. Pearson, Ottawa, Ontario. *Canadian Medical Association Journal*, 1920, vol. x, p. 916.

This course of treatment is offered to aid the general practitioner to avoid the dangers of inadequate treatment of syphilis on the one hand and of producing medicinal intoxication of the patient on the other. Continued treatment with mercury and potassium iodide alternating with rest intervals, with occasional injections of arsphenamine is the most effective method of controlling the disease. General tonics should be administered during the rest intervals to combat the toxic effects of the antisyphilitic treatment and to

raise the antibody production of the patient. This is as important as the actual treatment itself. Treatment for early primary syphilis should be continued for two years. Treatment for late primary and generalized syphilis should be continued for, at least, three years.

**The Intensive Administration of Arsphenamine.**—Herman Goodman, New York. New York Medical Journal, 1920, vol. cxii, p. 494.

Eighty hospitalized syphilitic negro men were given the intensive arsphenamine treatment as suggested by Pollitzer. The clinical results were immediate in all uncomplicated syphilitic manifestations. The infectiousness of the patient was reduced thereby much quicker than with the same amount of the arsphenamine introduced intravenously by the so-called intermittent method. The changes in serology were most encouraging, but no attempt is made to base conclusions on them. Reference to the former publications on this method will give information on this phase of the subject. With no further precaution than that taken for the administration of arsphenamine intermittently, the eighty men were given this intensive form of treatment with excellent results, and the author does not hesitate to recommend the procedure for more general use by those especially skilled in the application of arsphenamine as generally administered. The public health value of this method of therapy should be emphasized since the period of hospitalization of infectious syphilitic persons is much reduced. This is an important consideration in the prophylaxis of syphilis by treatment.

**Experimental Syphilis in the Rabbit.**—Wade H. Brown, Louise Pearce and William D. Witherbee, New York. Journal of Experimental Medicine, 1921, vol. xxxiii, p. 495.

From a study of a series of rabbits inoculated with two old strains of *Treponema pallidum*, it was found that localized infection of bones and tendons was of frequent occurrence and led to the formation of a variety of lesions. The bones usually involved were those of the face and the feet and legs. Most often the lesions arose from the periosteum but developed also within the bone or marrow cavities and at lines of epiphyseal union. Grossly, the periosteal lesions were of two types, one being a circumscribed, indurated, and nodular mass and the other a process of a more diffuse character. Histologically, the lesions presented the typical appearance of syphilitic granulomata composed of more or less distinct layers which corresponded roughly with structural divisions of the periosteum. The composition of lesions of membrane and of cartilage bones differed somewhat in this respect, especially in the development of an osteoclastic layer. Invasion of the bone with absorption and necrosis were constant features of periosteal affections and were most marked in the case of the facial bones and the small bones of the feet. Lesions in the bone and marrow cavities were detected chiefly by radiographs or by the occurrence of bone destruction in the absence of periosteal involvement. They were characterized by a loss of structural detail in the bone, rarefaction, in-

creased fragility, necrosis, pathologic fracture, and epiphyseal separation associated with more or less granulomatous reaction. Histologically, the bone lesions presented essentially the same picture as those of the periosteum, while the lesions which arose from the marrow cavities were composed chiefly of polyblastic infiltrations. In this group of affections, the most important were those which developed at the epiphyses. The destructive effects produced by all classes of lesions varied from a slight surface erosion or rarefaction to extensive necrosis resulting in the formation of bony defects or in disintegration or fracture of the bone. These conditions differed very decidedly with the particular bones involved. Of especial importance in this connection was the occurrence of a peculiar form of mass necrosis which at times resulted in the destruction of considerable areas of bone even in parts where the granulomatous type of lesion was comparatively slight. The most characteristic injuries were the saddle-nose deformities and the epiphyseal separation in the small bones of the tarsus and hind feet. The marks of permanent injury were, on the whole, comparatively slight, but they also differed both with the degree of the original injury and with the bone affected. Granulomatous lesions of tendons or tendon sheaths were occasionally seen, and in a few instances, lesions of synovial cavities were demonstrated microscopically.

**Experimental Syphilis in the Rabbit. Affections of Bone, Cartilage, Tendons, and Synovial Membranes. Part 3.**—Wade H. Brown, Louise Pearce and William D. Witherbee, New York, *Journal of Experimental Medicine*, 1921, vol. xxxiii, p. 525.

A systematic study was made of the affections of bone, cartilage, tendons, and synovial membranes which occurred in a series of rabbits with generalized syphilis. Localized infection of this group of structures was found to be of very frequent occurrence. The parts involved were, in the order of their frequency, the facial and cranial bones and cartilages, the bones, tendons, and joints of the feet and legs, the cervical and caudal vertebræ, the ribs, and the sternum. These infections often gave rise to characteristic manifestations of disease which could be detected without difficulty by inspection or palpation of the part. In many instances, however, clinical manifestations were so slight that the presence of lesions could be detected only by radiographic or pathologic examination. Detailed descriptions of various clinical types of disease were given and the clinical manifestations correlated with the pathologic process. It was pointed out that bone lesions exhibited a decided predilection for certain exposed bony prominences, for lines of bony union, and for epiphyseal lines in particular. A study of the clinical history of bone lesions brought out the fact that they were among the earliest of the generalized forms of disease; they tended to pursue a comparatively rapid course, and relapse was never observed. Especial emphasis was laid upon three aspects of the experimental infection: the analogy existing between certain forms of the animal and human affections, the relation of syphilis of the osseous system to other evidences of disease, and the occurrence of obscure bone lesions. In this connection, it was pointed out that the nasal and epiphyseal lesions of the rabbit presented a striking analogy to those of congenital



syphilis in man. It was also pointed out that syphilis of the osseous system occupied a definite position in the scheme of defensive reactions such that lesions of these tissues might be favored or inhibited according to the experimental conditions employed. Finally, the frequency with which infections occurred which were accompanied by sufficiently distinctive signs even to suggest the possibility of their existence was interpreted as evidence that some cases of latent or obscure infection in man might find their explanation in the presence of a similar group of affections.

**Experimental Production of Clinical Types of Syphilis in the Rabbit.**—Wade H. Brown and Louise Pearce, New York. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 254.

In the course of investigations dealing with generalized syphilis in the rabbit, it was noted that distinctly different types of disease were frequently produced by inoculations made with a given strain of *Spirocheta pallida*; it also appeared that there was an appreciable connection between the experimental conditions employed and the type of disease which occurred. Since it had been found possible to convert a disease which is usually localized into a generalized disease by diminishing or suppressing the primary reaction, it appeared that by modifying the reaction in different ways, one might produce types of disease which would conform to alterations in the defensive mechanism. Experiments carried out on a large series of animals showed that such was the case. By various experimental procedures, different types of infection were produced, and in this way it was found that there was a definite sequence of tissue involvement or of tissue reactions which made it possible to produce infection or to confer protection on a given group of tissues according to the nature of the means employed. From the manner in which the infection responded to modifications of the defensive reaction, the conclusion was drawn that a wide variation in the clinical type of the disease might be traceable to this one group of causes. This, of course, does not eliminate the possibility that variation in the biologic properties of the infecting organisms may contribute to further variations in the type of the disease.

**Experimental Syphilis in the Rabbit. Affections of Bone, Cartilage, Tendons, and Synovial Membranes. Part 2.**—Wade H. Brown, Louise Pearce and William D. Witherbee, New York. *Journal of Experimental Medicine*, 1921, vol. xxxiii, p. 515.

It was a notable feature of this group of lesions that they rarely led to extensive necrosis. Grossly, the surface of the bone was eroded or roughened, and obliteration or widening of the epiphyseal line could be demonstrated by use of x-rays. Similarly, when the lesion healed, the bone might show a slight roughening or increase in thickness with a few tiny nodes but rarely was there any considerable deviation from the normal. Microscopic examination showed, however, that the syphilitic process frequently extended through the entire thickness of the bone and that the effect produced was in general much greater than gross appearances would indicate.

**Multiple Primary Syphilis of the Hand.** Gaviati (Aiuto). *La Riforma Medica*, February 26, 1921, xxxvii, 9.

The author appears to regard this case as something very unusual but inasmuch as it was the result of a fracas with a companion who was notoriously syphilitic, during which the patient struck the other in the mouth with his fist, the latter being injured in several places by contact with the teeth, the episode cannot be regarded as especially novel, many such being on record. Some of the minor details of the case, however, present interest. The victim sustained three abrasions, two of which over the knuckles of the medius and third fingers respectively are readily intelligible, while the third, over the metacarpophalangeal joint of the thumb, is less readily understood. The incubation period was longer than usual. At the end of 7 weeks the scars at the seat of the abrasions were seen to be nodular, and as a result of some irritating local treatment ulcers formed *in situ*. These were soon succeeded by a general outbreak of eruption and an unusual degree of anemia and debility. There was no primary lesion on the penis but some mucous papules were found in the balano-preputial area. The epitrochlear lymphnode of the corresponding side was notably enlarged. The lesions on the hand were found to contain the treponema. The type of primary syphiloma was the ulcero-hypertrophic, all three lesions presenting it.

**The Incidence of Congenital Syphilis Among the Newly Born.**—S. M. Ross and A. F. Wright, Edinburg. *Lancet*, London, 1921, vol. i, p. 321.

It must be realized that the number of specimens dealt with is too small to draw any definite conclusions from, but the percentage of positive reactions obtained is significant and calls for further investigation in wider areas: first, among unselected cases, and secondly, from those where either parent is known to be infected, so that the reliability of the test may be definitely gauged from the results achieved. The latter investigation could easily be arranged in the lying-in homes of infected patients. When one takes into consideration that women in the latter stages of pregnancy tend to give a much less positive Wassermann reaction than the history of the case warrants, and that congenitally syphilitic babies tend to give a negative Wassermann reaction until a month or so after birth, whether the complement-deviating substance in the placental blood is indicative of syphilis in the mother and not according to Fildes in the child, or in the child and the mother according to Kolmer, the facts are that 3.5 per cent specimens of placental blood were found positive by two observers using entirely different methods in different laboratories, and the authors presume to repeat that these results are highly suggestive of the prevalence of apparently undiagnosed syphilis in the general population.

**Three Cases of Syphilitic Infection During Birth.**—Lomholt (Copenhagen). *Annales de dermatologie et de syphiligraphie*. January 1921, vi series, 2, 1.

This form of contagion, which in theory might seem not unusual, has very rarely been authenticated. In 1911 Haslund was able to locate but a single

(personal) case during the postspirochetic period. Naturally the mother must have an infectious lesion in the birth tract and the infant an abrasion to insure communication. The fact that the child of an infected mother is usually itself infected would help to make the accident a rare one. In the case cited by Haslund the infant was 5 weeks old when the primary lesion appeared—in this case lesions, for the port of entry was the forceps mark on the cheek and no less than 7 chancres formed in the latter. One year later Groen of Cristiana reported a similar case in which the infant showed multiple primary lesions of the scalp and here the number was no less than eleven.

The author himself has seen three more cases making a total of 5 Scandinavian cases. These have all been seen since 1917. The first child showed at the age of 6 weeks 5 primary lesions on the sinciput. Confrontation showed the mother in full secondary syphilis including moist papules on the genitals. The infant was otherwise robust and his seroreaction negative and after the inunction treatment was begun the reaction remained negative throughout. The labor was tedious and severe but there were no instruments used. In the second of the author's cases the labor was of the same sort, the mother showed papules on the genitals and the infant four weeks after delivery showed a number of primary lesions of the scalp. Seroreaction positive. The third infant showed 4 primary lesions on the vertex, mother apparently sound but later showed secondary lesions. The three mothers had all been infected by their husbands in the last month of gestation. In all of the cases the author was at great pains to exclude hereditary syphilis and there was never any doubt that the disease had been acquired *en passage*.

**Mitral Insufficiency, Polyarthritis and Syphilis.**—Attinger. Schweizerische medizinische Wochenschrift, April 7, 1921, li, 14.

The combination of rheumatism of the acute polyarthritic type involving the cardiac valves with syphilis is not very common and a case of this type should prove of interest. The patient, a man of 24, had suffered from polyarthritis some 6 or 7 years before and it was impossible to learn whether the mitral lesion developed as a sequel or had preexisted. Four years after the attack there was a recrudescence of the polyarthritis which was accompanied by pericarditis. The symptoms of the latter were severe for the time but resolution rapidly took place. The mitral lesion did not disqualify the man from light labor, and the original diagnosis of severe mitral insufficiency was modified. One year after the recurrence of rheumatism the man was found to have secondary syphilis, having been infected about a year before this rheumatic attack. He had received prompt mercurial injections and was placed by the author on intensive salvarsan-mercurial treatment. During 9 months of 1918 the author controlled the subject's heart and noted no difference in its status; but in the Fall of 1920 the condition was found to have undergone striking improvement. If the original endocarditis had dated back to early childhood during an overlooked attack of rheumatism, angina, etc., one would not have been surprised if the mitral lesion had undergone notable regression because such cases are not uncommon. Complete regression has even been seen.



In the absence of such an explanation we should be thrown back on the theory that the antisymphilitic treatment had been responsible for the amelioration which practically began after the author's intensive cure. This would necessitate the belief that syphilis had attacked the heart at a very early period in the form of a myocarditis.

**Splenomegaly of Syphilitic Origin.**—L. Queyrat (Paris). *Bulletin de la Société Française de Dermatologie et de Syphiligraphie*, 1921, 2.

Splenomegaly of syphilitic origin is rare as shown by the fact that some other factor able to explain the condition may almost always be found, while syphilis can usually be excluded. The author has had a case under observation for ten years. The patient who is now 51 years old was first seen in 1910 and at that period the abdominal enlargement was conspicuous because of the degree of emaciation present. The conclusion from palpation was that the woman had a greatly enlarged spleen. The liver was normal and there was no ascitic or other fluid in the peritoneal cavity. There was no pain or tenderness but considerable mechanical discomfort. The hypertrophy of the organ dated back at least three years. There was further no history of alcoholism or evidence of tuberculosis, no circulatory disturbance. A medical man had diagnosed leukemic spleen and had treated the woman without benefit with the x-rays. The diagnosis by exclusion was possible syphilitic splenomegaly and this was later borne out by a positive seroreaction. The blood formula was now taken and excluded leukemia. The patient was placed on an intensive inunction cure with KI and later was given a course of grey oil injections. But while her general condition was greatly improved thereby the spleen showed only a relative improvement. A course of arsenobenzol then followed with further reduction of the enlarged organ until an irreducible minimum was apparently reached. The seroreaction is still positive and the author believes that it will always remain so. In discussion Renault called attention to the fact that treatment with arsenobenzol sometimes caused splenomegaly and cited two personal cases of this kind. Goubeau had seen cases in young children with hereditary syphilis and thought syphilitic splenomegaly more common in the young child than in the adult.

**A Biologic Study of Latency in Syphilis.**—Martin F. Engman and Frederick Ebersson, St. Louis. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 347.

In this study *Spirocheta pallida* have been isolated in five instances from latent syphilitic patients—three times from inguinal glands (two female and one male) and twice from the semen. The strains produced typical syphilitic lesions in rabbits' testicles and could be recovered and propagated for an indefinite number of generations. The incubation periods of spirochetes isolated from the gland were, respectively, 50, 54 and 133 days, the last being doubtful owing to an early secondary infection in the experimental animal. The two strains which were isolated from the semen developed after four and seven months, respectively. *Spirocheta pallida* were isolated from patients who

gave a history of syphilis dating back eleven and thirteen years in two instances and one year in three instances. An inguinal gland and the semen proved positive for spirochetes in the two first cases mentioned and the glands and semen in the last named. In this series of positive results, a gland was found to be infectious in the case of a man whose Wassermann reaction had been negative, following treatment, and at the time of taking a specimen for the experiment gave a two-plus reaction in the cholesterol antigen only. A second instance of this nature was found in the case of a specimen of semen which proved positive for *Spirocheta pallida*. As far as studies with these different strains have progressed, there is no indication that *Spirocheta pallida* have lost in virulence for the rabbit. Detailed experiments on infectivity and other phases of experimental syphilis with these and other strains will be reported subsequently. It appears from this investigation and from that of others that the blood and other body fluids, excepting semen, are not infectious in latent syphilis, or if so, rarely. Incubation of blood from latent syphilitic patients did not favor any infectious property which might have existed. Thirty-six specimens, duplicates of those in the series, were incubated at 37° C. for from three days to four months before injection into rabbits' testicles. The results were negative. One-third of the total number of spinal fluids from latent syphilitic patients gave evidence of lymphocytosis, and one gave a positive Wassermann reaction. Tonsils could not be studied owing to severe secondary infections which were set up in the experimental animals. In one case, a dark-field examination showed what appeared to be *Spirocheta pallida* in an emulsion of a tonsil taken from a child with a family history of syphilis and himself giving a positive Wassermann reaction, although free from symptoms or visible lesions. The rabbits failed to survive injections of material. The groups studied were composed of untreated patients, as well as of those who had received no treatment within the past two years. Between the time of taking specimens for inoculations of rabbits and the first symptoms or a suggestive history of syphilis in these patients, from one to forty years had elapsed. Of a total of 500 cases of syphilis, which were seen at the clinic, seventy-five, or exactly 15 per cent, of the number were definitely latent. These investigations demonstrate the fact that those who give a history of a syphilitic infection may harbor active virulent *Spirocheta pallida* for years, and this in the face of irregular negative Wassermann reactions or slight reaction in the cholesterol antigen only.

**A Case of Vesical Syphilis.**—A. Boeckel (Strasbourg). *Journal d'urologie*, 1920, x, 5, 6.

Until recently the existence of vesical syphilis was denied, but of late years many cases have been reported, some of which are not entirely convincing. The patient was a woman aged 31, who was originally under treatment for gonorrhea with bilateral pyelonephritis. She also presented a gonorrheal metritis. Crises of cystitis developed from time to time and the cystoscope showed both vesical and pyelorenal infection. The trigon and neck of the bladder were highly congested, the remainder of the vesical cavity less so.

In the right periureteral region and fundus were strewn erythematous plaques the size of a lentil, the majority of roundish contour while a few only were oval. As the author had never seen any such picture in the cystoscope, he suspected syphilis. The woman denied infection but the seroreaction was positive. There were no treponemata in the urine. Under injections of salvarsan and cyanate of mercury the lesions soon vanished.

**Frambesia of the Mucosæ.**—P. Noel (Cameroun). *Annales de dermatologie et de syphiligraphie*, February, 1921, vi, series 2, 2.

The claim that the mucosæ are almost never attacked in yaws has served in the past to exclude the possibility of syphilis in doubtful cases. The author, who is physician-major in the French Colonial troops, begins by quoting from current authorities. One speaks of the massing of lesions about the mucocutaneous orifices and mentions ulcerative rhino-pharyngitis. Another saw but one case of implication of the throat in 128 patients. A third states that the yaws never begin on any mucous surface. The consensus of opinion is that very rarely the mucosæ may be attacked primarily. One writer quotes Castellani to the effect that yaws often causes lesions like mucous patches, but the author has been unable to locate this passage. Thus far the author writes of early yaws. The fact that late ulcerous and destructive lesions attack the rhino-pharyngeal and contiguous mucosæ has generally been admitted, although it has been discovered in recent times that such lesions are frequently not yaws at all but due to syphilis or some fungus. The same type of destructive lesion in Brazil has been attributed to the spirochete of yaws, to the blastomycetes and to the leishmania, all three organisms having been found by bacteriologists. The treatment test is of great value in these cases, for if due to yaws the lesions yield readily to potassium iodide, while the others are refractory to all treatment.

The author has studied 100 cases of yaws in Cameroun, the sex incidence being nearly the same (51 men, 49 women). Nearly all were under the age of 30. The greatest number of primary lesions was upon the lower extremities, then in order on the upper extremities and genitals, face and trunk. The scalp was the seat of lesions in 20 per cent, although this area is usually spared. Passing by orificial lesions the author found lesions of the mucosæ in 37 cases out of 100 and predominantly in the female. Age played no role in the incidence. There were lesions of the buccal mucosa in 22, of the nasal mucosa 19, and of the conjunctiva in 4, and in a number of the patients all three localities were attacked. None of the lesions could have been primary and chiefly they were of very early appearance. The purely mucous lesions were essentially papillomatous, round or oval, with sharp contours. Elsewhere the author speaks of the close resemblance between the artificial lesions of yaws and syphilis but apparently the resemblance between the mucous lesions of yaws and mucous patches is not so striking. The papillomatous aspect serves to distinguish them. They may disappear spontaneously and yield readily to treatment and there is apparently none of the obstinacy seen at times in syphilitic lesions of the same type. In none of the author's cases were there lesions which could be



called tertiary and as far as Cameroun is concerned the mutilating rhinopharyngitis of authors is not to be seen and presumably is due to another organism than the *pertenus*.

**Twelve Cases of Pulmonary Syphilis.**—Berisso and Adelardi (Buenos Aires).

Revista Sud-Americana de Endocrinologia, Immunologia y Quimioterapia, January 15, 1921, iv, 1.

These cases were all treated in the medical clinic of the Italian Hospital of Buenos Aires. Pulmonary syphilis almost always develops in the tertiary period but the authors have known it to appear 4 and 6 months respectively after the primary lesion. But syphilis not uncommonly appears at a very early period in the bronchi, trachea and larynx. In the authors' series of cases the male was the usual victim and the right lung suffered more than the left. In 70 per cent there was syphilitic aortitis. Tertiary syphilis of the lung may be acute or chronic, the former being very rare and simulating lobar or bronchopneumonia. No less than 10 varieties of the chronic form have been isolated as the frankly gummatous or tumorous, the pseudotuberculous, the pseudopneumonic, syphilitic bronchiectasis, syphilitic pleuritis, tracheobronchial adenopathy of syphilitic nature, involvement of the lung in general visceral syphilis, syphilitic pulmonary gangrene, association of syphilis and tuberculosis and syphilitic bronchial asthma. In regard to the possibility of cure some cases responded well to treatment, others ineffectually. The best results were seen in bronchial lesions and next in order were the pleural and in general the gummatous forms, third the sclerogenous forms and last of all the caseous form, the two last classes being presumably irrecoverable. Nevertheless but one patient died and there was no case which did not show an initial response to treatment. The latter comprised intravenous salvarsan and mercury and iodide of potassium by the mouth. A distinction is made between sclerogummatous and sclerous processes without antecedent gumma formation. The former yielded well to treatment while the latter evidently refers to fibrosis of the pulmonary tissue.

**Raynaud's Disease and Syphilis.**—Ghelfi (Parma). La Riforma Medica, Feb. 12, 1921, xxxvii, 7.

Some years ago the author reported a case of Raynaud's disease which appeared to be due to an attack of influenza. Since that period he has seen two others in which there was evidence of syphilitic causation. The first patient was a young woman who had never been seriously ill. The lesions suggested beginning Raynaud's disease and a vasotonic regimen was prescribed, comprising at different times adrenaline, hypophysine, ergotine, cold baths, etc. The cutaneous symptoms were not favorably influenced. In addition there were general symptoms not ordinarily encountered in this affection which suggested cerebral implication so that lumbar puncture was practiced and the punctate gave a positive Wassermann reaction. Alongside the other symptoms there had been a progressive failure of health and loss of weight. Injections of calomel and neosalvarsan were begun and after four months' time the

symptoms, including the cyanotic condition of the extremities, had nearly disappeared. The slight mental inferiority present had preceded the outbreak of the disease. Some years elapsed before a similar case was encountered—in a woman of 38, who for a year had been suffering from painful, cold and cyanotic extremities. The diagnosis was made of Raynaud's disease while the seroreaction for syphilis was positive both for the blood and spinal fluid. The x-ray showed no implication of the skeleton. The suspicion and confirmation of the existence of syphilis were the outcome of the author's recollection of his first case. After one month's specific treatment the patient suddenly left the hospital and at a later period gangrene developed in one of the limbs, requiring amputation.

**Clinical Observations on Overlooked Syphilis of the Nose, Throat, Larynx and Ear.**—Bilancioni (Rome). *Giornale di Medicina Militare*, March 1, 1921, lxi, 3.

The author writes at great length on his theme and narrates many case histories. The material comes from the ear, nose and throat clinic of the University of Rome and the author admits that he has nothing really new to communicate. He discusses overlooked syphilis in general with reference to its great frequency. The percentage in the male is about 20 and in the female as high as 56, according to one statistician, but in some of the special clinics these figures, high as they are, are much too low. Thus in a class for eye diseases in a certain dispensary the per cent of ignored syphilis in men was 52 and that in women 86. In the author's clinic phenomena like leukoplakia buccalis, disturbances of audition, vertigo and nervous deafness, speech disturbances, etc., at once suggest possible syphilis. Intranasal cases are sometimes seen as in the case of a woman of sportive proclivities whose syphilis was masked under the cocaine habit. She sniffed as much as 15 grams daily and for a year had had in addition to general evidences of cocaineism, intranasal disorders which she blamed upon her drug habit. These included perforation of the septum. She was found to have an osteoperiostitis gummosa of the vomer and vault of the nose. But syphilis had been excluded in two dermatologic clinics apparently without a Wassermann test, which in the author's hands proved positive. The patient was readily cured with salvarsan. Syphilis of the mouth and throat is often overlooked. There are certain predisposing factors which should serve to put us on guard in this particular. Thus those who irritate the mucosa by the free use of tobacco, alcohol, spices and other local irritants should be especially investigated, while certain authors believe that the so-called arthritic temperament predisposes to this localization. The following lesions have to be borne in mind in the latter. In addition to the manifestations of active syphilis we have cicatrices, perforations and distortions due to the healing of ulcers and in the third place leukoplasic lesions which, while not at all specific, are very often seen on a syphilitic background. Finally cancer is apt to develop not only from leukoplakia but more rarely from syphilitic scars, or in the margin of unhealed ulcers. It is perhaps the one area in the body in which syphilis is undoubtedly

a forerunner of cancer. Pansinusitis may be a manifestation of ignored syphilis and the author relates a number of cases. For some reason he fails to mention so-called syphilitic ozena. While true ozena is practically never seen in syphilis, several ozena-like conditions are not uncommon, including the depression of the bridge of the nose; and the author's comments under this head would have proved of interest. In none of the cases given of pan- and polysinusitis is there any mention of fetor of the breath. Space does not suffice to quote from the description and cases of ear disease, deafness, vertigo, etc., or from the sections on laryngitis and tracheobronchitis.

**Pupillary and Reflex Disturbances in Two Hundred and Seventy-Five Cases of Neurosyphilis.**—Lawson G. Lowrey, Boston, and Mary K. Benedict, New York. *Journal of Nervous and Mental Disease*, 1920, vol. lii, p. 106.

In 70 per cent of 275 cases of neurosyphilis the authors find some type of abnormal pupillary reaction: in 50 per cent a stiff pupil and in 40 per cent the Argyll-Robertson pupil. The Argyll-Robertson pupil occurs more frequently in tabes and in taboparesis than in paresis. In 70 per cent of all cases they find some abnormality of the tendon jerks, rather more than half of these showing diminished or absent jerks. These are our most accurate clinical signs of neurosyphilis. They are often equivocal. Hence the importance of lumbar puncture in the diagnosis of nervous and mental diseases.

**Alcohol and Syphilis as Causes of Mental Disease.**—George H. Kirby, New York. *Journal of the American Medical Association*, 1921, lxxvi, p. 1062.

Psychoses due to syphilis reached the highest point of which we have a record in the year 1918. Since then a decline in the relative and actual number of cases has occurred which, in view of the increase of population, may be regarded as at least a hopeful sign. Whether or not the more thorough and scientific treatment of syphilis in its early stages will bring about a further reduction of neurosyphilis and syphilitic psychoses, is a question to be answered in the future. From the standpoint of mental hygiene, the situation may be regarded as encouraging. A notable advance has been made in the direction of controlling one of the outstanding causes of mental disease, namely, alcoholism, and as regards a second great cause of mental disease, namely, syphilis, there are indications that education, prophylaxis and improved methods of treatment are beginning to yield some results, as yet slight, to be sure, but nevertheless sufficient to be considered a sign of progress.

**Acute Syphilitic Nephritis.**—Joseph A. Elliott and Lester C. Todd, Charlotte, N. C. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 634.

Acute syphilitic nephritis is an infrequent complication of syphilis. The diagnosis depends on: (a) the existence of any early syphilis; (b) the high albumin content of the urine with a relatively small number of casts; (c) therapeutic tests. This case fulfilled these requirements. Arsphenamine is the drug of choice in treating this condition. An initial dose of from 0.15



gm. to 0.25 gm. may be given. The subsequent doses may be gradually increased. The maximum dose given this patient was 0.4 gm. The authors believe that mercury should not be used until after the disappearance of the albumin from the urine, as advocated by Stokes.

**Visceral Syphilis.**—H. E. Marchbanks, Pittsburg, Kansas. *Journal of the Kansas Medical Society*, 1920, vol. xx, p. 320.

Tumors in the epigastric region should not be diagnosed until a blood Wassermann has been made. Visceral syphilis is found most frequently in the third decade. A negative history does not rule it out. Complete physical examination is essential for the diagnosis of obscure abdominal symptoms, and such examination is not complete without a Wassermann.

**Diseases of the Eye Due to Syphilis and Trypanosomiasis Among the Negroes of Africa.**—J. N. Roy, Montreal, Canada. *Archives of Ophthalmology*, 1921, vol. 1, p. 28.

Africa has not been the cradle of syphilis. This affection coming from Asia, has first ravaged the populations of the northeast and the north of this continent, and then has been transmitted to the blacks. Later on, at different epochs, the pox has shown up on the coast, brought over especially by the Europeans. In sleeping sickness, alterations of the eyes are seldom met with in the blacks of Africa. With them, this organ resists very well to this infection, much more than with trypanosomized animals, who often show ocular lesions. In syphilis, the affections of the eye are most frequently found in the anterior segment, and are less frequent with the blacks than with the whites—as also observed in human trypanosomiasis. The nervous system of the blacks appears to have never presented any specific manifestations. Some African tribes seem to have a certain state of immunity against the pox, which is very slight with them, and this immunity has already struck me in Asia, and in South America.

**Juvenile Tabes.**—Charles Rosenheck, New York. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 572.

Juvenile tabes may be considered a distinct clinical entity in view of the long accepted dictum that adults alone were subject to the disease. That the creation of separate entities in a disease that affects both young and old may be justly criticized as being clinically confusing and scientifically unsound is not denied; but in view of the rarity of its occurrence and the special characteristics of the affection in the young, juvenile tabes is deserving of special recognition. Juvenile tabes is the result of an hereditary syphilitic infection in the great majority of cases. An insignificant number of cases are due to syphilis acquired during infancy. Its symptomatology differs in no way from that of the adult type, but special characteristics in its onset and course are worthy of note. Early visual difficulties proceeding to blindness and optic atrophy are characteristic of fully 40 per cent of the cases. Lancing pains,

ataxia, and visceral or vesical disturbances affect only a small number. Trophic disorders are absent. Females are particularly vulnerable to the affection; as twice as many girls show the disease as boys. The ratio in the adult type is placed as ten men to one woman. The prognosis is excellent for life, but extremely poor for vision.

**Congenital Syphilitic Epiphysitis in Adolescence.**—E. J. Gaenslen and Wm. Thalheimer, Milwaukee, Wisc. *Journal of Orthopedic Surgery*, 1921, vol. iii, p. 8.

This lesion in the greater trochanter of the femur the author believes to be a manifestation of congenital syphilis. The findings on which he bases this opinion are as follows: 1. The predominance of cartilage and the riotous appearance of the process of osteogenesis. 2. The lack of completion of bone formation. 3. The excess of calcium deposit in the cartilage which is in apposition with the areas of bone formation. 4. The obliterating endarteritis in the thickened periosteum. Stains for spirocheta could not be made because the process of decalcification which was necessary prevented the use of methods for staining spirocheta.

**The Diagnosis of Primary Syphilis.**—Henry D. Lloyd, Boston. *Boston Medical and Surgical Journal*, 1920, vol. clxxxiii, p. 540.

One of the most important factors, if not the most important, in the successful diagnosis of primary syphilis is a lesion which has not been treated either with silver nitrate or some form of mercury. In a series of 97 consecutive cases a positive diagnosis was made in 96 per cent by means of the dark-field microscope. In a number of these cases, however, repeated examinations were necessary. The positivity of the Wassermann test, which at the end of ten days averages about 30 to 35 per cent, increases to practically 100 per cent at the end of the fifth week after the appearance of the chancre. By employing careful clinical observation and both laboratory methods of examination, repeatedly if necessary, but few cases of primary syphilis should go unrecognized.

**The Whys and Wherefores of Unreliable Wassermann Reports.**—William Krauss, Memphis, Tenn. *Southern Medical Journal*, 1921, vol. xiv, p. 186.

Technical workers who are not trained immunologists and have not a science degree of some kind, which fits them for understanding immunologic principles, should never be left to their own devices. They need a foreman. The field should be accessible only to those who in the course of training show an inherent unshakable conscientiousness and sense of accuracy. The slightest symptoms of any tendency to "sloppiness" or other evidence of undesirability should work their instant dismissal. The keynote to laboratory diagnosis is accuracy. The employment of technicians incapable of delivering accurate, dependable work is an unpardonable culpability and should be dealt with in no uncertain manner.

**A Short Silver Impregnation Method for the Demonstration of Spirochete Pallida in Tissue.**—Samuel R. Haythorn, Pittsburgh. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 725.

The picture obtained by the use of the acetone silver method is practically the same as that obtained with Levaditi's method. The spirochetes appear very black, and in a few instances positive results were obtained with the acetone silver infiltration when Levaditi's method was negative. The great advantage of the method is that it may be carried out within three days, and when the fresh tissue is received early in the morning, it may be made ready for examination on the second day following.

**Ice Water-Bath in Complement Fixation for the Wassermann Reaction—A Shortened Technic.** W. W. Duke, Kansas City, Mo. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vi, p. 392.

The use of an ice water bath for one hour for complement fixation for the Wassermann test gives as complete a degree of complement fixation as incubation in the ice box for four hours. The use of an ice water bath, therefore, shortens the refrigeration technic three hours without altering its accuracy. For this reason its use is recommended.

**Comparative Values of Complement-Fixation Methods in Syphilis.**—Howard D. McIntyre, Emerson A. North and Aurelia P. McIntyre, Cincinnati, Ohio. *Journal of Laboratory and Clinical Medicine*, 1921, vol. vi, p. 233.

Cholesterinized antigen properly prepared and titrated yields from 10 to 15 per cent more positive Wassermann reactions on luetic sera than does the plain antigen. We consider it a perfectly safe antigen to employ in the Wassermann reaction with complement fixation in the ice box at 2° C. for a period not longer than ten hours, observing the precautions outlined in this paper. We have obtained but one positive reaction employing such methods in which the clinical findings, the history, or both, did not justify a diagnosis of lues. We may say here that we still have this patient under observation and there is a great possibility which may be later established that this patient has had lues. The Hecht-Gradwohl test when positive in the temperate zone is diagnostic of lues. It will yield 15 per cent more positive reactions on luetic sera than does the classical Wassermann reaction. It may be employed in from 95 to 98 per cent of fresh sera (not over forty-eight hours old). It does not yield false positive results in tuberculosis. The Wassermann test employing complement fixation in the ice box at 2° C. will yield a much higher percentage of positive reactions than does the Hecht-Gradwohl test employing complement fixation in the water-bath. With complement fixation under the same conditions, however, the tests practically agree. The three serologic reactions appear in the serum and disappear under treatment in the following order: The ice box Wassermann reaction is the first to appear positive, the Hecht-Gradwohl test follows, the water-bath Wassermann reaction appearing last. Under treatment the water-bath Wassermann reaction disappears first, the Hecht-Gradwohl reaction next, the ice box Wassermann reaction last.



**Interpretation of Wassermann Reaction of Blood Serum in Mental Diseases.—**

J. Allen Jackson and Horace Victor Pike, Danville, Pa. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 360.

A positive Wassermann reaction of the blood serum alone indicates nothing further than that the individual has come in some manner in contact with syphilis, either hereditary or acquired. It does not mean that the mental disorder from which he suffers is due to syphilis. A diagnosis of neurosyphilis should be based on definite neurologic signs and spinal fluid reactions, irrespective of the readings of the blood serum. Psychoses in which there is a positive Wassermann reaction of the blood serum, but showing no other serologic, neurologic or clinical evidences of syphilis do not demand antisyphilitic treatment for the reason that such treatment will not modify the mental condition, furthermore, neurosyphilis is seldom, if ever, superimposed on a well developed psychosis. General systemic syphilis as shown by a history of infection, clinical signs and positive Wassermann reaction of the blood serum should be treated as such, but not with the view of favorably influencing the psychosis. Antisyphilitic treatment avails nothing in well advanced cases of general paresis or tabes dorsalis. Cerebral, cerebrospinal and spinal syphilis are amenable to treatment and antisyphilitic therapy should be pushed to the limit. Successful treatment of neurosyphilis resolves itself into the early recognition and therapeutics of the infection, and lies largely in the hands of the general practitioner and syphilographer; all syphilitics should be kept under routine observation for a period of at least ten years in order that vigorous treatment may be instituted at the first signs of involvement of the central nervous system.

**Curve of One Thousand Four Hundred Wassermann Reactions After Treatment**

**by Neoarsphenamine and Mercury Salicylate.—**Keith M. B. Simon, Belize, British Honduras. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 639.

The chart is compiled from 1,400 tests, about 700 patients being examined. A blood test was usually made on admission if the patient had not been tested serologically previously in some other laboratory. The second blood test was usually made after the primary lesions had disappeared in early primary cases, or on completion of the first course. If the patients gave a positive Wassermann reaction after seven injections of neoarsphenamine and nine injections of mercury, at least a month was allowed to elapse before a second course was instituted. After obtaining a negative reaction these cases could not be further followed as the men were returned to their units or sent home for discharge. If a rash or secondary symptoms were also present, the case was considered a secondary one. The curve on the chart shows that it took from two to eleven injections to obtain a negative Wassermann reaction in primary cases; secondary cases required from seven to twenty-two. The minimum number of injections for a primary case was two, for a secondary, seven; the maximum number of injections for primary cases was fourteen, and for secondary twenty-two. Tertiary cases never gave a negative reaction

while under treatment in the clinic, but a diminution of fixation was invariably noted. The technic used for the Wassermann reaction was the No. 4 method recommended by the Medical Research Committee of the United Kingdom.

**Concerning the Specificity of Cholesterinized Antigens in the Serologic Diagnosis of Syphilis.**—Robert A. Kilduffe, Pittsburgh. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 598.

All Wassermann reactions should include at least three antigens of varying delicacy: preferably a cholesterinized extract of human heart, an extract of acetone-insoluble lipoids, and an alcoholic extract of syphilitic fetal liver. Wassermann reports should give the antigens used, the reaction to each, and the interpretation of the reaction as a whole, with, perhaps, the dose of serum tested and the method of fixation. Reactions with cholesterinized antigens of 4-plus or 3-plus degree are indicative of the presence of syphilitic "reagin" in the blood. Reactions with cholesterinized antigens below the grade of 3-plus should be looked on as suspicious and as indicating the necessity for further investigations and should not be looked on as invariably false or proteotropic fixations. Syphilitic patients under treatment should remain under observation until complement-fixation tests are repeatedly negative to cholesterinized extracts, not only with the blood serum but, if possible, with the spinal fluid.

**The Sachs-Georgi Precipitation Test for Syphilis.**—Thomas G. Hull and Eva E. Faught, Chicago. *Journal of Immunology*, 1920, vol. v, p. 521.

A modification of the Sachs-Georgi precipitation test for syphilis is described, using clear blood serum and an alcoholic extract of beef heart, either cholesterinized or not. The precipitation test agreed with the Wassermann test in 88 per cent of the cases; in 7 per cent it was more delicate, giving positive results where the Wassermann was negative; in 3 per cent it was negative where the Wassermann was doubtful; in 2 per cent it was negative where the Wassermann was positive. Treatment of the patient apparently affects the results of the precipitation causing it at times to become negative while the Wassermann still is positive. Attempts to determine whether the precipitate formed in this test was entirely responsible for the Wassermann reaction were unsuccessful.

**The Wassermann Reaction: Its Uses and Abuses.**—Crawford Lundie. *South African Medical Record*, 1920, vol. xviii, p. 342.

A negative test is no proof that a patient is free from disease, but, coupled with negative clinical evidence, it is a useful confirmation of the negative diagnosis. A positive test is not in itself sufficient ground for putting a patient on treatment. It is a useful confirmation of doubtful clinical evidence. A clinically positive case that has treatment before the reaction was positive, and never develops a positive reaction, is probably cured without the disease

having become generalized. A case with a positive reaction may become negative on treatment, but the reaction may again become positive, so that a negative reaction in a case where it has once been positive is no certain proof of cure, though the case may be cured. A continued positive reaction, in spite of treatment, is no proof of active disease in absence of clinical signs. It may merely indicate the continued production of immune bodies. An increasingly positive reaction, on the other hand, indicates active disease, and calls for treatment, even in absence of clinical signs. An appearance of or increase in a positive reaction after a dose of 606 or 914 is an indication of the presence of active disease, and calls for treatment. A woman who has had syphilis may always infect her unborn children, and should have treatment during each pregnancy.

**A Comparison of the Wassermann and Sachs-Georgi Reactions in the Serologic Diagnosis of Syphilis.**—Robert A. Kilduffe, Pittsburgh. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 415.

A diagnosis of syphilis, or a conclusion as to treatment, cannot be based on the results of a Sachs-Georgi test with safety, and the reaction is not suitable for general use for this purpose.

**The Sachs-Georgi Reaction for Syphilis.**—S. A. Levinson and W. F. Petersen, Chicago. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 286.

An examination of 1,042 serums and cerebrospinal fluids by means of the Wassermann and the Sachs-Georgi reactions demonstrated a close parallelism of the two reactions (92 per cent). In sixty-two cases in which the Wassermann reaction was negative while the Sachs-Georgi reaction was positive or doubtful, the clinical history or examination revealed evidence of syphilis in 58 per cent. The technic of the Sachs-Georgi reaction is simple, only one biologic reagent is required (antigen) instead of the four used in the Wassermann test (antigen,amboceptor, complement and red blood cells). This simplicity adds to the uniformity of the results. The ultimate specificity depends on the preparation of a proper antigen. Because of its simplicity, and the fact that it is frequently positive in syphilitic cases when the Wassermann test is negative, the authors are of the opinion that the Sachs-Georgi reaction offers a valuable aid in the routine examination for syphilis when used in conjunction with the Wassermann reaction.

**Experiments with the Flocculation Test (Sachs-Georgi) for Syphilis.**—W. R. Logan, Edinburgh, Scotland. *Lancet*, London, 1921, vol. cc, p. 14.

Under conditions as outlined, results can usually be obtained by the flocculation test, which approximate closely to those of careful Wassermann tests, and in the author's hands the most accurate and most easily read were obtained when turbid emulsions were used rather than the opalescent solutions advocated by Sachs and Georgi, and when a considerably longer period of incubation was made use of than their standard time of 18 to 20 hours. It



must be admitted, on the other hand, that the series of false positives already referred to occurred when these thick emulsions were being used, and it is possible that the increase in the surface of the suspended lipoids carries with its advantages this particular danger. He believes, however, that on this occasion the cleaning of the glassware had been insufficient. When opalescent solutions are used, the readings seem to be too difficult and too liable to cause the introduction of a personal element, and for this reason it is desirable that the comparatively gross flocculation seen with the thicker emulsions should be aimed at in standardizing the test. Until the factors which may cause false reactions are definitely recognized and can be controlled the test should not be used to supplant the Wassermann reaction, although it may profitably be used as an additional control to that test. Even when used in this way at least half a dozen negative and half a dozen positive controls should always be included. Further experiments into the nature of the reaction are in progress.

**The Effect of Antisymphilitic Treatment on the Colloidal Gold Reaction.**—Margaret Warwick, Minneapolis. *Archives of Internal Medicine*, 1921, vol. xxvii, p. 238.

The colloidal gold reaction shows a tendency to decrease under the influence of antisymphilitic treatment, but may remain unchanged or even increase in intensity. The more pronounced the colloidal gold curve the less it is affected by treatment. On the other hand, the lower curves are more readily brought down to normal. A positive colloidal gold curve may be of diagnostic value in cases having received previous treatment, but a negative reaction is of less significance. A "provocative" reaction may appear in the spinal fluid as well as in the blood Wassermann as a result of the institution of treatment. The colloidal gold reaction does not parallel or follow the clinical symptoms of the progression or regression of the disease. If the colloidal gold curve changes after treatment, it increases or decreases in intensity and occasionally drops back into another zone, but is usually a symmetrical curve and does not become atypical. The Nonne and Wassermann reactions tend to parallel the colloidal gold curve in its behavior to treatment and in the provocative reaction. The cell count is increased only in spinal fluids from cases showing affection of the central nervous system, but even in such cases it is not always constant and bears very little relationship to the other routine tests or to clinical signs, improvement or provocative reactions.

**Discrepancies Between the Clinical Symptoms and Laboratory Findings in Syphilitic Disease of the Nervous System.**—George A. Moleen, Denver, *Colorado Medicine*, 1920, vol. xvii, p. 147.

Definite syphilitic lesions of the nervous system may exist when the blood serum and spinal fluid show no complement fixation with the various modifications of standardized antigens. Positive returns in the blood and spinal fluid may be obtained in cases in which the clinical manifestations of nervous lesions are wanting. Most important are the changes in the colloidal gold reaction

of Lange, and their presence is to be valued even in spite of negative Wassermann reactions in the serum or cerebrospinal fluid. The number of cells is to be regarded as contributory evidence, and especially important with reference to syphilis (or tuberculosis) when the greater percentage of cells are small mononuclear lymphocytes. All laboratory procedures must be valued only as contributory evidence, as modifying, but not contradictory to, clinical phenomena—that the preponderating evidence belongs to clinical manifestations of disease. It must be clearly stated that in the absence of clinical evidence of a nervous lesion, the presence of a positive Wassermann reaction is not to be ignored, inasmuch as lipoids giving such a reaction may exist in the body fluids, probably derived from sequestered or isolated foci, without or prior to, the occurrence of disintegrative lesions of the nerve structures.

**New Procedure for the Prevention of Spinal Puncture Headache.**—Gustav Baar, Portland, Oregon. *Medical Record*, 1920, vol. xcviii, p. 598.

The prophylactic value of these intravenous injections of 0.5 per cent NaCl 500 to 750 c.c., may also be gleaned from the fact, that four cases when spinal puncture was done without being followed by 0.5 per cent NaCl, suffered from headaches for two to sixty days, while if followed immediately by the salt solution these same cases developed no headaches.

**The Cerebrospinal Fluid in Treated Syphilis.**—Joseph Earle Moore, Baltimore. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 769.

Study of the spinal fluid should be carried out as a routine in all syphilitic patients, as an essential to intelligent treatment. Spinal puncture should be performed after the first or second course of arsphenamine, and should be repeated at least once before the patient is discharged as presumably cured. If this is done in every case of syphilis, and treatment intelligently administered according to the results obtained, the incidence of clinical neurosyphilis may be reduced to an absolute minimum.

**Iodine in the Cerebrospinal Fluid.**—Earl D. Osborne, Rochester, Minn. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1384.

Iodine is present in the cerebrospinal fluid of normal individuals. Iodine, in increased amounts, is present in the cerebrospinal fluid following the administration of iodides by mouth, by rectum and intravenously. The iodine content of the cerebrospinal fluid following administration of iodide by mouth or by rectum is small compared with that following the administration intravenously. The iodine content of the cerebrospinal fluid following the administration of iodide intravenously plots a definite curve, depending on the amount administered. Certain observations made in the course of this study suggest the possibility that (a) neurosyphilitic tissue takes up more iodine than normal nervous tissue, and (b) the presence of a meningitis increases the permeability of the meninges to iodine compounds in the blood.

**A Study of the Spinal Fluid in One Thousand Eight Hundred and Sixty-Nine Cases of Syphilis in All Stages.**—Udo J. Wile and C. H. Marshall, Ann Arbor, Mich. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 272.

The nervous system, if uninvolved as shown by the accepted criteria during the first months of the infection, is seldom invaded later. A negative preliminary puncture followed by positive findings at a later date occurred in only three of several thousand cases punctured. Of the several criteria indicating involvement, the increase of organic solids is found to be slightly higher than either the cell count or the Wassermann reaction, the relative value being indicated in the order just mentioned. A considerable degree of cerebrospinal involvement may be present in the latent period of syphilis without manifesting any signs or symptoms. Such asymptomatic cases may become symptomatic later, and a study of the colloidal gold curve in these cases is of some value in estimating the ultimate prognosis of the case. Comparing the large number of cases of primary and secondary syphilis in which positive findings are found, with the relatively small percentage of late neurosyphilis as compared to total syphilitic incidence, we must conclude that a large number of early cases are in the nature of a meningeal roseola, which is transitory in its clinical aspects. The interpretation of the lumbar puncture findings, particularly early in the incidence of the disease, constitutes a valuable guide in estimating the ultimate prognosis of the disease with regard to the integrity of the nervous system.

**Superinfection in Experimental Syphilis Following the Administration of Subcurative Doses of Arsphenamine or Neoarsphenamine.**—Wade H. Brown and Louise Pearce, New York. *Journal of Experimental Medicine*, 1921, vol. xxxiii, p. 553.

Experiments were carried out on rabbits for the purpose of determining the effects of subcurative doses of arsphenamine and of neoarsphenamine upon the resistance of infected animals to reinoculation with *Treponema pallidum* and hence the possibilities of the occurrence of a second infection in treated but uncured cases of infection. All the animals used were inoculated with the same virus, and the experimental tests were carried out when the first cycle of testicular reaction was nearing its height. The animals with the most marked testicular lesions were used for the basic experiment of treatment and reinoculation. The results of this experiment were controlled from four different standpoints: (1) the effect of the treatment employed upon the existing infection; (2) the immunity present at the time of treatment; (3) the virulence of the organisms used for reinoculation as compared with those causing the existing infection; (4) the comparative susceptibility of normal animals to the virus used for reinoculation. The results obtained showed (1) that the treatment employed was insufficient to cure any of the therapeutic controls; (2) that the infected controls were highly refractory to a second inoculation; (3) that the treated animals were highly susceptible to a second inoculation and although not cured of their original infection, reacted to the



second inoculation with the formation of lesions indistinguishable from those of a first infection; (4) that in certain instances the treatment given had rendered infected animals more susceptible to infection than the normal controls.

**Severe and Fatal Cases of Mercurial Stomatitis.** Gerard-Maurel and Renard (Paris). *Revue de stomatologie*, December, 1920, xxii, 12.

The authors describe two cases of mercurial stomatitis, one of which ended fatally while the other was followed by extensive necrosis of the mandible. The former occurred in a woman of 64 with apparent tuberculosis although without positive bacillary finds. It was learned that she was an old syphilitic and inferred that the pulmonary lesions were of that nature. There was a sclerous syphilitic glossitis and the teeth—what remained of them—were in wretched condition. She received a course of 15 biniiodide injections in small dosage without any evidence of mercurialism. At this juncture an attack of Vincent's angina supervened. This was treated locally with neosalvarsan but became aggravated, while a gingivitis of the same nature was superadded. The condition resisted injections of the same medicament and the patient was transferred to the hospital where it was noted that an insupportable gangrenous odor came from the mouth. There had taken place a sloughing of the faucial tissues, gums and internal aspects of the cheeks. It was believed that osseous tissue was also implicated. As neosalvarsan, the specific for Vincent's disease, had failed to check the affection surgical treatment was begun. The remaining teeth were extracted and the necrotic area eurented. The upper jaws were found involved, the maxillary sinuses being open. A sequester was removed from the right side. The entire area was irrigated and treated with zinc chloride, but with only transient benefit. Death took place 22 days after the first appearance of the angina.

The second patient was a young woman with comparatively recent syphilis who had received courses of intravenous injections of cyanate of mercury and neosalvarsan followed by a few single injections of grey oil. Then mercurial stomatitis developed for the first time and three weeks had elapsed before the patient was seen by the authors. The picture in this case, unlike the first, was typical. There were salivation, tenderness of the gums and buccal ulcers. The tongue was swollen and eating solid food was impossible. Cultures showed an abundance of Vincent's fuso-spirillary association mingled with other microorganisms. As the milder measures were without effect it was thought possible that a syphilitic component was present and neosalvarsan was begun again in the hope of affecting favorably the Vincent or syphilitic component. At the fifth intravenous injection a nitritoid crisis occurred without the slightest improvement having been noted. The condition became progressively worse and symptoms pointed to necrosis along the inside of the cheeks. Under general anesthesia surgical treatment was applied to the buccal cavity. The teeth which had become loosened were extracted. It then became apparent that the upper and lower jaws were both necrotic. Several weeks were required for the sequesters to come away, these in the mandible being extensive. The

patient made a good recovery after this experience. In commenting on the cases the authors state that in all severe mercurial stomatitis Vincent's infection plays a prominent part, although the metal is the primary cause. If the cases had represented only a Vincent infection neosalvarsan should have favorably influenced them.

**Some Experiments on the Volatilization and Absorption of Mercury.**—C. E. Jenkins. *British Journal of Dermatology and Syphilis*, 1921, vol. xxxiii, p. 135.

The rate of volatilization of mercury at blood-heat is insignificant. In the inunction method of administering mercury the metal is absorbed through the skin.

**A Study of the Histologic Changes Produced Experimentally in Rabbits by Mercurial Compounds.**—John A. Kolmer and Baldwin Lucke, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 531.

The administration to rabbits of different soluble and insoluble mercurial compounds commonly employed in the treatment of syphilis, by intramuscular and intravenous injection, inunction and oral administration, and in amounts analogous to the maximum doses given to human beings, resulted in the production of tissue changes in all organs examined, namely, the brain, heart, lungs, spleen, liver and kidneys. The most conspicuous changes were found in the brain in the nature of perivascular round cell infiltrations, and in the kidneys, as tubular and capsular glomerulonephroses of varying degrees of severity. Details of the histologic changes in these and the other organs included in this study are described. The degree of tissue injury caused by the different preparations of mercury appears to bear a direct relation to the actual amounts of pure mercury absorbed irrespective of the kind of preparation and route of administration.

**Some Factors Relating to the Toxic Action of Arsphenamine.**—Reid Hunt, Boston. *Journal of The American Medical Association*, 1921, vol. lxxvi, p. 854.

The symptoms (in rats) caused by m-amino-p-hydroxyphenylarsenous oxid ("arsenoxid") are very characteristic; the presence in arsphenamine of a percentage of the "oxide" too small to increase greatly the toxicity can readily be detected by the symptoms; confirmatory evidence of the presence of the "oxide" (or of some oxidation product of arsphenamine) in a toxic preparation of arsphenamine is obtained by treating the solution with sodium hydrosulphite: this leads to an immediate diminution of the toxicity if the latter is due to the presence of the "oxide." No toxic commercial preparations of arsphenamine have been encountered, the toxicity of which could be attributed to the presence of the "oxide." Some preparations of arsphenamine are very toxic when the solutions are prepared at ordinary room temperature; the toxicity is greatly reduced by gently warming and in some cases by allow-

ing the solutions to stand for a time at room temperature. Cold may preserve the toxicity for long periods. (Preparations which, after warming, may be tolerated in doses of 150 mg. per kilogram may kill in doses of 60 mg. before warming.) It is considered probable that the undue toxicity of such preparations is due to the physical state of the solution, and that this undergoes a rapid change when the solution is warmed. Toxic preparations of arsphenamine are sometimes encountered, the toxicity of which is due to factors other than the foregoing: the toxicity is not diminished by the action of sodium hydro-sulphite or by warming; it is not due to inorganic arsenic and certain other compounds which have been suggested.

**A Study of Arsphenamine-Serum Precipitates and Their Relation to Clinical Reactions.**—Jay Frank Schamberg, K. Tokuda and John A. Kolmer, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 263.

The amount of alkali in the solutions of arsphenamine has great influence on the reactions following the mixture of a serum and arsphenamine in test tube, with solutions of neoarsphenamine. Negative results were similarly more precipitates than the disodium solutions because the latter contain an excess of alkali. Furthermore, all precipitates, including those produced when acid solutions of arsphenamine are mixed with serums, can be dissolved at once by the addition of a few drops of a normal solution of sodium hydroxid. This constitutes proof that the precipitate is a drug precipitate and not a protein precipitate, because a protein precipitate could not be redissolved in this manner. The amount of alkali in the solutions of neoarsphenamine may have a similar relation to the results observed when solutions are mixed with serums. The results observed in these experiments indicated that the solution of some lots of neoarsphenamine produced more positive reactions than other lots; furthermore, the addition of a single drop of normal sodium hydroxide immediately dissolved the precipitates and yielded clear solutions. The serums of patients exhibiting immediate nitritoid-reactions after neoarsphenamine did not form precipitates when brought in contact, in the test tube, with solutions of neoarsphenamine. Negative results were similarly obtained with the serums of patients who had febrile and gastrointestinal reactions. Test tube precipitates of arsphenamine occurred as frequently and as pronouncedly with the serums of patients not exhibiting febrile and gastrointestinal reactions after arsphenamine as with the serums of those who did manifest such reactions. As practically no nitritoid reactions occurred after arsphenamine during the period of their study, the serums of such patients could not be tested. In so far as the results observed with the serums of patients showing immediate (nitritoid) reactions after the administration of neoarsphenamine are concerned they found no evidence to support the deductions of Berman that these simple tests will serve to foretell the occurrence of these reactions, although it must be stated that Berman's tests were conducted with the serums of patients who had "nitritoid" reactions after the administration of arsphenamine. It is highly probable that the reactions observed when serums and solutions of arsphenamine and neoars-



phenamine are mixed in test tubes, are primarily dependent on the amount of alkali present in the solutions or in the serums. The amount of alkali present in different lots of arsphenamine and neoarsphenamine is likely to vary and thereby influence the occurrence of precipitates with different lots of the drugs and the serums of patients. These precipitates are largely composed of arsphenamine or neoarsphenamine rather than of serum proteins, and are readily dissolved by the addition of traces of sodium hydroxide.

**Prevention of Acute Arsphenamine Reaction by Antianaphylaxis and Atropine.**—George J. Busman, Rochester, Minn. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1302.

The exact nature of nitritoid and gastrointestinal reactions to arsphenamine is undetermined. It seems not improbable that a variety of causes may act to produce a single syndrome of which the acute reaction on the table, and in certain cases, the late gastrointestinal reaction may be phases of the same phenomena. In the group of cases herein reported, repeated nitritoid crises, associated with repeated gastrointestinal reaction, persisted regardless of any controllable factor in the technic. Repeated uncontrollable acute reactions are interpreted as personal idiosyncrasies of the patients to the drug. The observation of Stokes on the value of atropine and of induced antianaphylaxis (Besredka technic) in the control of a persistent tendency to acute nitritoid crisis is confirmed. It has been further found that a tendency to repeated late gastrointestinal reaction can also be controlled in a large number of cases by either method alone, or by a combination of the two methods. Atrophine is sometimes effective in doses less than one-fiftieth grain. A combination of the use of atropine and the induction of antianaphylaxis by dividing the dose of arsphenamine is more effective than the employment of either method alone. A combination of the two methods may make possible the continuance of arsphenamine treatment in patients in whom repeated severe reaction would otherwise force its abandonment.

**Salvarsan Falsifications.** H. Hunziker (Basel). *Schweizerische medizinische Wochenschrift*, April 14, 1921, li, 15.

Following the scarcity of drugs during the war profiteering and adulteration were seen to be rife especially in drugs which are regarded as indispensable—morphine, cocaine, salvarsan and the like. They were peddled about in restaurants, they were made the subject of speculation, those who dealt in them often had no knowledge of pharmacy and were easily imposed on by regular dealers. The author gives photographs of grossly counterfeited salvarsan which was found on analysis to be a mixture of barium sulphate and lead chromate. Another specimen consisted of a mixture of sand and rye meal colored with ochre and lead chromate. In other words there was some indifferent powder colored by admixture of a yellow substance. There was always an attempt to imitate the original package more or less closely, but comparison of different samples would have shown wide differences. These imitations were often represented as smuggled over the border from Germany into Switzerland. To one familiar with the

regular package the imitations must seem clumsy in the extreme. Had dealers known anything of the product the fraud could readily have been exposed by exposing the supposed salvarsan to the air for the genuine article turns brown from oxidation, while the substitutes do not change color. After the close of the war the evil persisted a long time and was slow in dying out.

**The Bulb in the "606" Apparatus.**—Captain J. H. Whiteside, R.A.M.C. *Journal of the Royal Army Medical Corps*, 1920, vol. xxxv, p. 406.

The use of a bulbous window in place of the usual straight one near the Harrison tap in the "606" apparatus relieves the administrator of any anxiety regarding the injection of air into the veins, as if there should be any air left in the tubes after the usual manipulations for expelling it, it is quite impossible for it to get past the bulb. Any bubbles of air coming down the tube find their way to the top of the bulb. Until the air becomes so great in quantity that it gets high in the bulb it is impossible for it to pass to the needle. Any air in the bulb can be easily expelled by holding the needle up with the tap open. The apparatus is extremely simple and cheap. To prove the truth of the above allow some air to pass down the tube and watch the effect. A convenient size of bulb is three-fourths inch outside measurement. The apparatus should lie in a horizontal position.

**Some Observations on the Treatment of Syphilis.**—William K. Trimble, Kansas City, Mo. *Journal of the Missouri State Medical Association*, 1920, vol. xvii, p. 94.

In the treatment of syphilis we are placing too much faith in the specificity of drugs. We are as a rule giving drugs too much with the idea in view of forcing a specific cure. In our treatment we give too little consideration to the immune processes that must take place. Syphilis cannot be cured and the best treatment is that which will give the patient the longest lease on life and usefulness to himself and society.

**The Treatment of Syphilis as Practiced in the United States Public Health Service Clinics of Indiana.**—F. W. Cregor, Indianapolis. *Journal of the Indiana State Medical Association*, 1920, vol. xiii, p. 266.

The medical profession should take an uncompromising stand for the full and complete treatment of syphilis. This can best be done by full co-operation with the lawfully constituted health organizations of the country. Syphilis may be aborted if encountered before five weeks have elapsed from the contraction of the disease. Syphilis may be cured by one year of treatment providing it is encountered before it has found lodgment in the tissues of the host. Syphilitics may be assured that they will remain free of symptoms, providing they fully cooperate in the treatment. The Wassermann should be employed as an aid and a comfort, and not as a guide and a control for action. As full cooperation is impossible in the face of ignorance of the disease and its potentialities, it is necessary that the patient be apprised fully and honestly of these things. Steps should be taken to reclaim the neurosyphilitic, possibly through the insane in-

stitutions, until such time as public enlightenment will relieve the present demand. A spinal Wassermann should be made in all cases before the case is discharged.

**Influence of Sulpharsenol on the Wassermann Reaction in Syphilis.**—Duroeux (Paris). *La Progrès Médical*, April 9, 1921, xlix, 15.

The author who has a service in the St. Lazare Hospital has been using this drug since February, 1919, the date of its introduction into practice. The earlier reports of those who tested it were conservative, but latterly reports have been more enthusiastic including those of English authors. Emery of Paris has been using the drug for 15 months and judging from its action on the Wassermann reaction it is regarded as a very active remedy. The injections have usually been given small and frequently repeated and this is rather burdensome on the physician. The author has spaced the injections so that the intervals are progressively longer. The total number in a month was then nine with a pause of about three weeks and a second series following. This alternation is continued, one series every two months, until there is reason to believe that the seroreaction is permanently negative. In the closely approximated injections the seroreaction became negative after the first series of injections in 87 per cent of 124 cases. In the longer spaced series the percentage was but 68 per cent in 164 cases, and in a number of cases a second and even a third series of injections was required to obtain the negative result. On a basis of 16000 injections the author would state that dose for dose sulpharsenol is superior by far to 914 and equal to 606. The seroreactions in both Wassermann and Hecht tests rapidly become negative in a good majority of cases. Once a negative reaction is obtained it has been permanent, although the observation period is too short for generalizations on this score.

**A Study of the Histologic Changes Produced Experimentally in Rabbits by Arsphenamine.**—John A. Kolmer and Baldwin Lucke, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 483.

The intravenous injection of lethal doses of acid nonneutralized solutions of arsphenamine in experimental animals produces widespread and severe vascular injury characterized by congestion, thrombus formation and hemorrhage; later cellular degeneration and necrosis take place. The intravenous injection of single large doses of solutions of disodium arsphenamine (ten times larger than the maximum amount administered to human beings at one time) produce severe vascular and tissue alterations, particularly in the liver, kidney, suprarenals and spleen. The intravenous injections of multiple therapeutic doses of solutions of disodium arsphenamine corresponding to doses of 0.6 gm. per 60 kilos of body weight, produce inconspicuous tissue alterations that do not appear to be sufficiently pronounced to interfere with the functions of the organs. Detailed descriptions of the histologic changes found in the brain and meninges, heart, lungs, liver, kidneys, suprarenals and spleen are given. These changes were induced by arsphenamine prepared by several different laboratories. These histopathologic changes probably bear an important relation to arsphenamine reactions and to methods of arsphenamine therapy.



**A Study of the Histologic Changes Produced Experimentally in Rabbits by Neoarsphenamine.**—John A. Kolmer and Baldwin Lucke, Philadelphia. *Archives of Dermatology*, 1921, vol. iii, p. 515.

The intravenous injection of single massive and multiple smaller doses of neoarsphenamine into rats and rabbits produces vascular injury, cellular degenerations and necrosis similar to those produced by solutions of disodium arsphenamine. The histologic changes found in the cerebrum, cerebellum, brain stem, meninges, heart, lungs, liver, kidneys, suprarenals and spleen are described. The tissue changes produced by neoarsphenamine are less severe than those produced by solutions of disodium arsphenamine when considered in relation to dosage per kilo of body weight. The changes described were produced in equal degree and with equal frequency by neoarsphenamine prepared by different laboratories.

**The Spirocheticidal Value of Disodium Ethyl Arsinat (Mon-Arsone).**—Henry J. Nichols, Washington, D. C. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1335.

Disodium ethyl arsinat, or mon-arsone, tested on rabbits infected with syphilis shows no spirocheticidal power. The tissues are fatally poisoned as soon as, or before, the spirochetes are affected. For its practical use in syphilis there is no such germicidal basis as exists in case of the arsphenamine group.

**Rectal Injection of Massive Doses of Neoarsphenamine.**—Henry G. Mehrtens, San Francisco. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 574.

Neoarsphenamine can be safely given intrarectally, in doses as large as 4 gm. Arsenic is absorbed into the blood after such injections, and larger quantities are eliminated in the urine than after ordinary intravenous injections of arsphenamine. Arsenic persists longer in the blood in perceptible quantities after the rectal method with large doses than after ordinary intravenous methods. About equal concentrations in the spinal fluid are obtained with either method.

## BOOK NOTICES

(Books for review should be sent to Dr. W. H. Deaderick, Associate Editor, Dugan-Stuart Bldg., Hot Springs, Arkansas.)

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**SYPHILIS, A TREATISE ON ETIOLOGY, PATHOLOGY, DIAGNOSIS, PROGNOSIS, PROPHYLAXIS AND TREATMENT.**—By Henry H. Hazen, A.B., M.D., Professor of Dermatology and Syphilology, Medical Department of Georgetown University; Professor of Dermatology and Syphilology, Medical Department of Howard University; Visiting Dermatologist and Syphilologist to Georgetown University; etc. With 160 illustrations including 16 figures in colors. 647 pages. St. Louis, C. V. Mosby Company, 1919. Price \$7.50.

Hazen, the author of this valuable work, has been fortunate in getting various syphilologists to contribute special chapters. Rea-soner contributed the section on Infection and Immunity; Fowler treated the subject of Syphilis of the Male Genito-Urinary Organs; Dunlop has written the major portion of the chapter upon the Bones, Joints, Muscles, Tendons and Bursæ; Lind the subject of the Central Nervous System; Dabney, the Ear; and Greene, the Eye; Craig, the Wassermann Reaction; Schamberg has written on the toxicology and Therapeutic Testing of Arsphenamine; Schweringen contributed to the subject of Radiographic Diagnosis; and Reede assisted in the chapter on the Endocrine Glands. The arrangement of the book from etiology to treatment is such as to enhance its value for ready reference. The technic of the Wassermann is so succinctly put that it is a practical laboratory guide. The feature of special chapters by eminent specialists makes the work a most valuable system of syphilis. The author's discussion of treatment is strictly modern and sane throughout.

**DERMATOLOGY, THE ESSENTIALS OF CUTANEOUS MEDICINE.**—By Walter James Highman, M.D., Associate Professor of Dermatology, New York Postgraduate Medical School and Hospital; Acting Associate Dermatologist, Mt. Sinai Hospital; Adjunct Dermatologist, Lenox Hill Hospital; Pathologist, Department of Dermatology,

Vanderbilt Clinic; etc. With 95 photographic illustrations. 482 Pages. New York, The MacMillan Company, 1921.

While the author holds that another reference work on dermatology would have no justification he states that works on cutaneous diseases usually ignore the teaching needs of beginners and that the present volume is dedicated, in spirit, to the novice, the general practitioner and those too busy to grapple with technicalities and abstractions. Literary citations, histologic descriptions, and elaborate historical sketches have been omitted, though nothing germane has been sacrificed. The work represents the author's conception of the minimum requisite for an adequate outline of the subject. As to therapy the author has described only what has commended itself to him through personal experience. Highman takes the broad view that the true dermatologist is the internist who knows the skin and this view is reflected throughout the work which exceeds the modest aims of the author and can be highly recommended to anyone interested in dermatology.



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## Original Articles

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### THE DIFFERENTIAL DIAGNOSIS OF CHANCRE AND CARCINOMA OF THE CERVIX

BY ALDRED SCOTT WARTHIN, M.D., ANN ARBOR, MICH., AND  
LLOYD NOLAND, M.D., BIRMINGHAM, ALA.

(Received for publication, June 11, 1921.)

SYPHILITIC lesions of the cervix of the uterus are frequently mistaken clinically for carcinoma, as pointed out by Gellhorn and Ehrenfest<sup>1</sup> in their very thorough review of the literature of genital syphilis in the female. Their collection of case reports includes six cases of primary chancre and fourteen of gumma of the cervix incorrectly diagnosed as carcinoma. They regard the correct differentiation between syphilis and carcinoma of the cervix as by far the most important problem connected with syphilis of the female genitalia. Other writers agree with this, and mention instances of errors in diagnosis not recognized until the patient was on the operating table or until later developments showed the presence of syphilis after amputation of the cervix or hysterectomy. Thibierge,<sup>2</sup> quoted by the above-mentioned authors, even expresses the opinion that many so-called cancers of the cervix recorded as permanently cured by operation, were in all probability syphilitic lesions.



Our own experience leads us to agree with Gellhorn and Ehrenfest as to the importance of the problem of the differential diagnosis of syphilitic lesions of the cervix. During the last six years there have been sent to the Pathological Laboratory of the University of Michigan eight cases of chancre of the cervix and six of late syphilitic lesions in the same location, and not in any one was a clinical suspicion of syphilis entertained. One of them was a hysterectomy for supposed carcinoma, four others were amputations and the remaining were diagnostic excisions of the cervix for suspected malignancy. On the other hand we have never had in our diagnostic service any case of carcinoma of the cervix incorrectly diagnosed clinically as syphilis. Very few cases of this form of error are recorded in the literature, although Wegscheider<sup>3</sup> reports two instances, in one of which the dermatologist, who mistook a carcinoma of the cervix for a luetic ulcer, was sued by the patient for malpractice. On the other hand we have examined a number of cases of simple erosion and ulceration of the cervix in which there had been a clinical diagnosis of syphilis.

We wish to record here a case of primary syphilis of the cervix in which the clinical appearances were so convincingly those of carcinoma, that a total hysterectomy was performed. Following the patient's discharge from the hospital, cutaneous lesions appeared in connection with a positive Wassermann reaction. The patient then brought suit for damages on the ground that she had been infected with syphilis while in the hospital, and her husband who at the same time showed signs of syphilis brought suit also for damages on the grounds that he had received his infection from his wife. The case is interesting, not only from the clinical and medico-legal aspects, but also because of the opportunity afforded by the material obtained from it to make a more thorough study of the pathology of primary uterine syphilis than the literature records at the present time.

*Clinical History.*—Mrs. P. H., white, aged forty-two, was admitted to the Employees' Hospital of the Tennessee Coal, Iron and Railroad Company, on October 13, 1920.

*Family History.*—Mother died of heart trouble. Father died of meningitis. Two brothers and one sister stillborn. History of grandparents not known.

*Past History.*—Usual diseases of childhood. Pneumonia in childhood. Influenza in 1919. For twenty-one years the patient has had dysmenorrhea. Has

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Fig. 1.—Chancre of cervix. Surface erosion. Infiltration of submucosa.

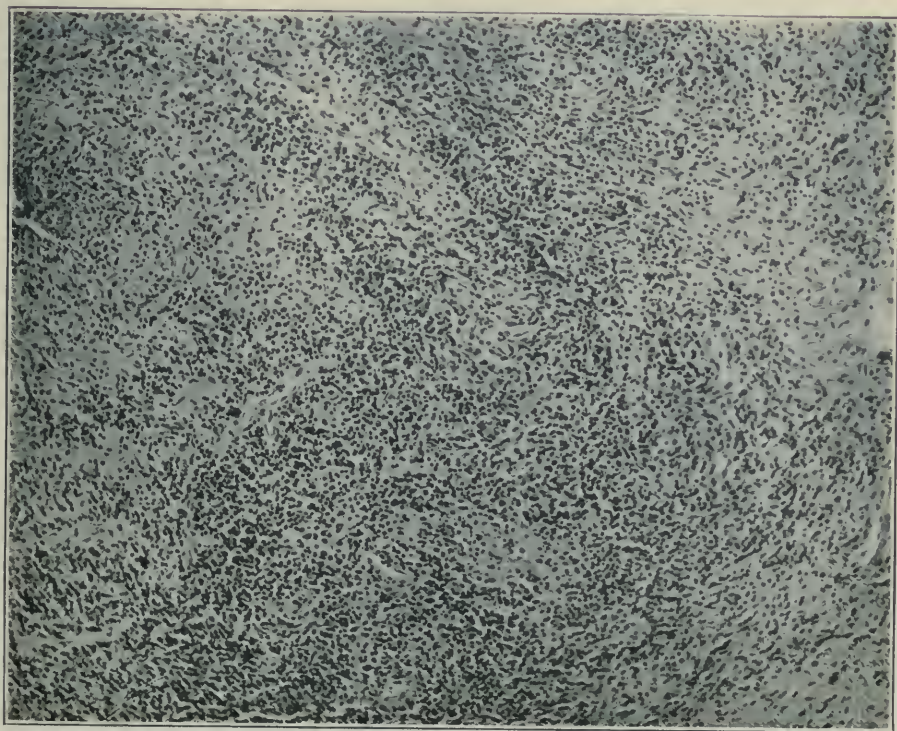


Fig. 2.—Chancre of cervix. Second zone from surface. Diffuse infiltration of the tissue-spaces around the small vessels.





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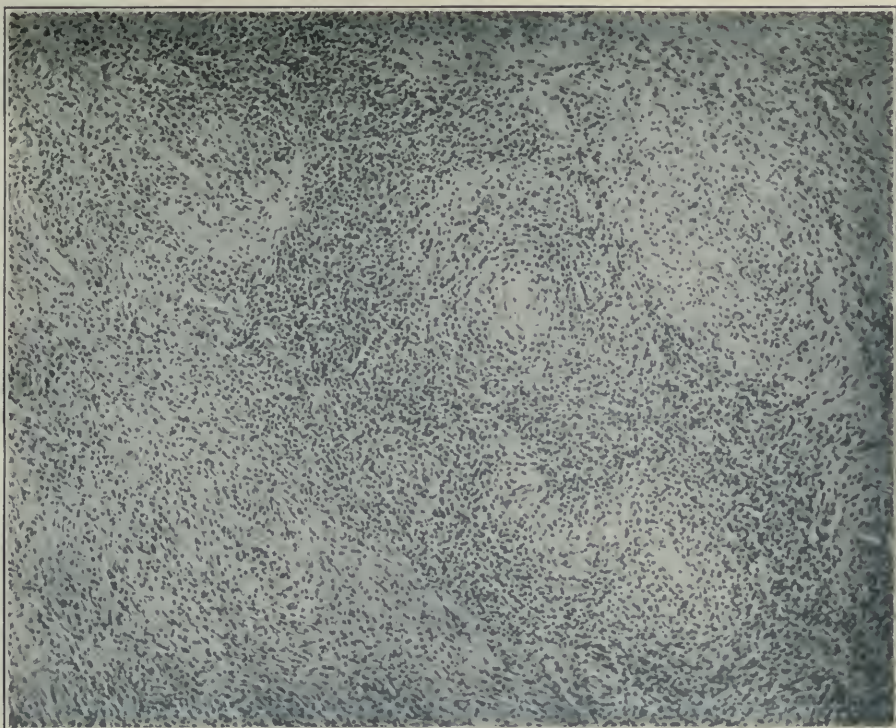


Fig. 3.—Chancre of cervix. Third zone from surface. Larger vessels with characteristic perivascular infiltrations.

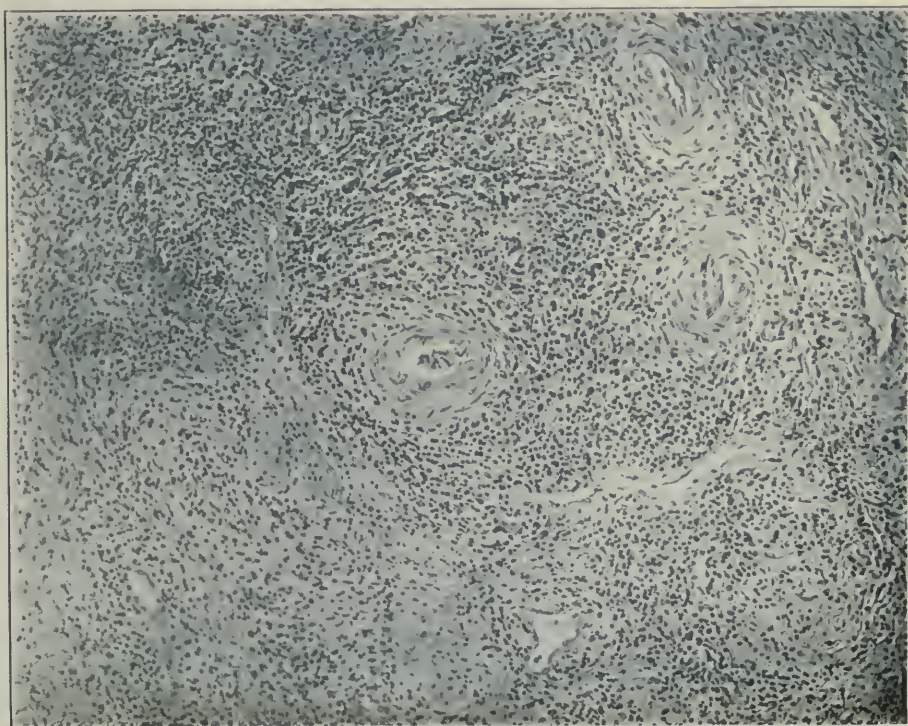


Fig. 4.—Chancre of cervix. Fourth zone from surface. Larger thick-walled vessels with infiltrations of the intervening tissues, around the veins and smaller vessels.



been subject to headaches all of her life. Has been married twenty-three years. Has two living children, youngest nineteen years of age. Has had no miscarriages and no stillbirths.

*Menstrual History.*—First menstruation at twelve years of age. Very regular. Duration three to four days. Always has pain for first two days. Last menstruation September 8, 1920, duration six days. Has had marked leucorrhea for about three years.

*Present Illness.*—Twelve days ago, October 1, 1920, the patient had a very severe headache, followed by a chill in twenty-four hours. The headache has been almost constant, and she has had six mild chills in twelve days, all of them in the afternoon. Temperature has not been taken in that time. On September 8, menstruation began. Patient complains of severe headache, backache, hot flashes and extreme nervousness, with constant pain in the lower abdomen and with frequent urination, but no tenesmus.

*Physical Examination.*—Poorly nourished, but fairly well developed white woman. The head and neck negative, except for palpable cervical glands. Heart normal, lungs negative. Abdomen, no rigidity, no palpable glands. Reflexes normal. Inguinal glands palpable. Epitrochlears palpable, but not greatly enlarged.

*Vaginal Examination.*—Some relaxation, not marked. Severe leucorrhea. The cervix shows a cauliflower ulceration, covering the entire surface. There is marked induration. The ulcer is partly covered by a dense adherent gray membrane, and bleeds on slightest touch. The uterus is retroverted, adherent and somewhat enlarged. Adnexa apparently normal. The patient complains of intense pain on examination.

*Urine Examination.*—Albumin negative. Sugar negative. No casts. Pus XX. Wassermann taken on day of admission (October, 13, 1920) was reported negative on October 17, 1920. No excision was made from the cervix for pathologic examination.

*Diagnosis.*—Ulcerative cervicitis and endometritis, with probable carcinoma of cervix.

Total hysterectomy was advised and on October 19, 1920, was performed under gas oxygen anesthesia. The patient made a very satisfactory recovery and was discharged from the hospital November 8, 1921, in very good condition.

On December 18, 1920, Mrs. H. reported back to the Out-Patient Department of the Hospital, complaining of an eruption on the arms and chest. The eruption was typically luetic. Blood specimen was immediately taken and was reported as anticomplementary. A second specimen taken a few days later was also anticomplementary. A third specimen taken on December 23, 1920, was reported as one hundred per cent positive. The patient was put on treatment, which was kept up for some weeks at the hospital, but she refused to continue treatment at the hospital, and sought medical advice elsewhere.

Pathologic diagnosis reported by hospital pathologist on October 26, 1920, from sections taken from the cervix and body of uterus was as follows: Chronic marked ulcerative cervicitis and endometritis. Nature of infective agent is not discernible. No evidence at all of malignancy."



About the middle of February, 1921, this patient entered suit against the hospital for the sum of \$100,000.00, claiming that she had been infected with syphilis in the taking of a Wassermann specimen at the hospital on October 13, 1920. Apparently, her claim was based on the fact that the first appearance of secondary syphilis was most marked on the flexor surface of the forearm in the region where the vein puncture was made.

The case came to trial in the United States Court, in Birmingham, on March 25, 1921. Mrs. H. testified in court that she had never had symptoms of syphilis before her admission to hospital. Her contention, through her attorney, was that she had had carcinoma of the cervix and was operated on for that condition. Mrs. H. testified that the first eruption appeared on the flexor surface of the right forearm on November 1st, one week before her discharge from the hospital and eighteen days after the blood specimen had been taken.

No evidence was produced as to the condition of the husband, but it is our understanding that he has syphilis, and as far as we can discover his symptoms developed subsequent to those of his wife, although this is not positive. He also has entered suit for \$100,000.00 damages on the ground of having been infected from his wife.

Fortunately the uterus had been preserved in ten per cent formalin, and at the time of the threatened suit, was sent, February 1, 1921, to the Pathological Laboratory of the University of Michigan, in Ann Arbor, for pathologic examination and diagnosis, the pathologist being asked to examine for evidences of malignancy.

*Gross Appearances.*—After three months in formalin the cervix still showed well the appearances that had been clinically interpreted as carcinoma. It was enlarged, indurated, irregularly nodular or cauliflower-like, its surface showing a shallow ulceration covered with a thin, grayish membrane, about the size of a silver dollar, completely encircling the external os, but more nodular on the anterior lip. It involved the entire vaginal portion. The consistency was very hard, without crumbling. On section the erosion was found to be very shallow, not deeper than the loss of the surface epithelium. Beneath this the cervical tissues showed a uniform dense and firm infiltration throughout. The uterus was enlarged, as compared to its average resting state at this age; it contained sev-

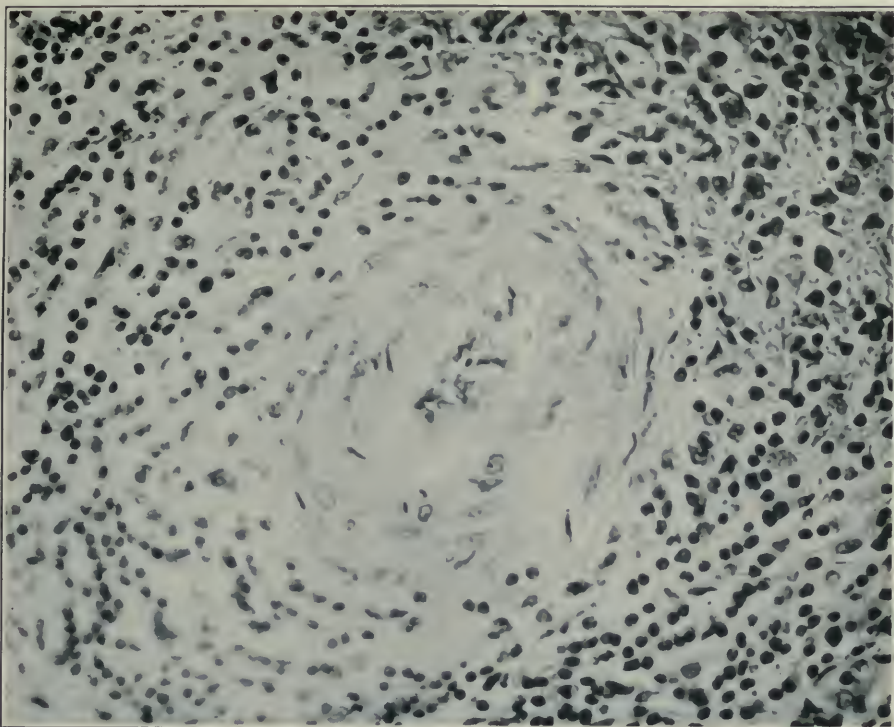


Fig. 5.—Chancre of cervix. High power view of arteriole from fourth zone, showing the plasma-cell infiltrations of the perivascular spaces.

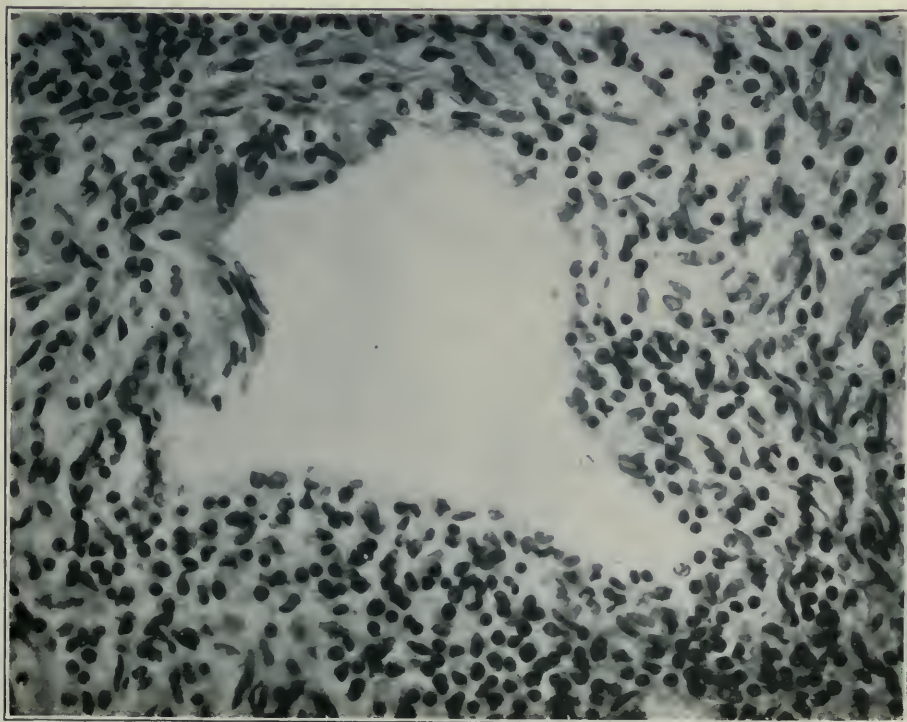


Fig. 6.—Chancre of cervix. Venous space from fourth zone. High power showing plasma-cell infiltration of vessel wall.





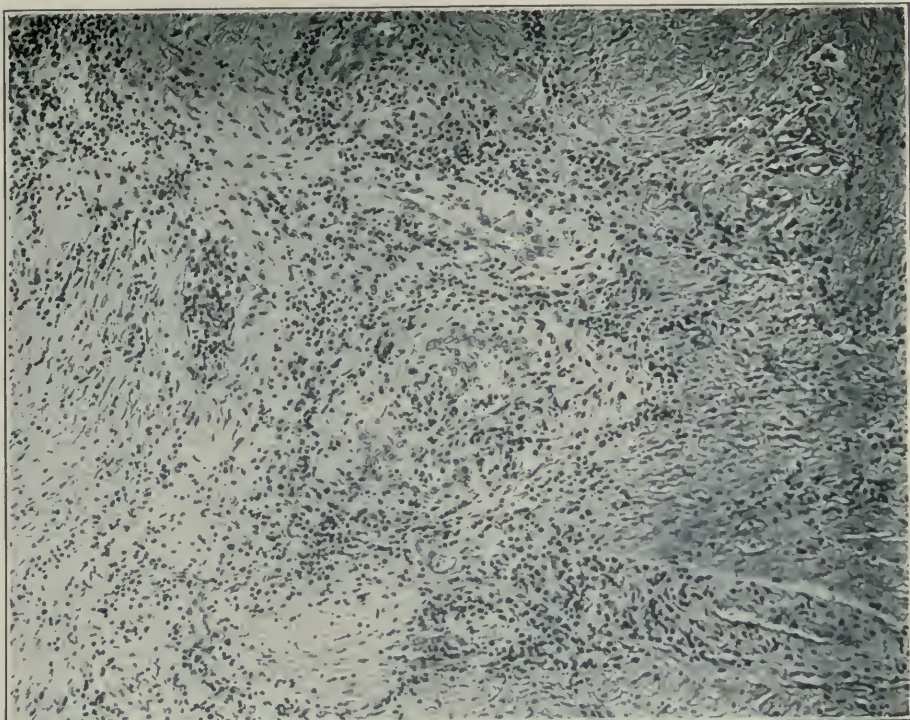


Fig. 7.—Chancre of cervix. Plasma-cell infiltrations in the musculature of cervix.

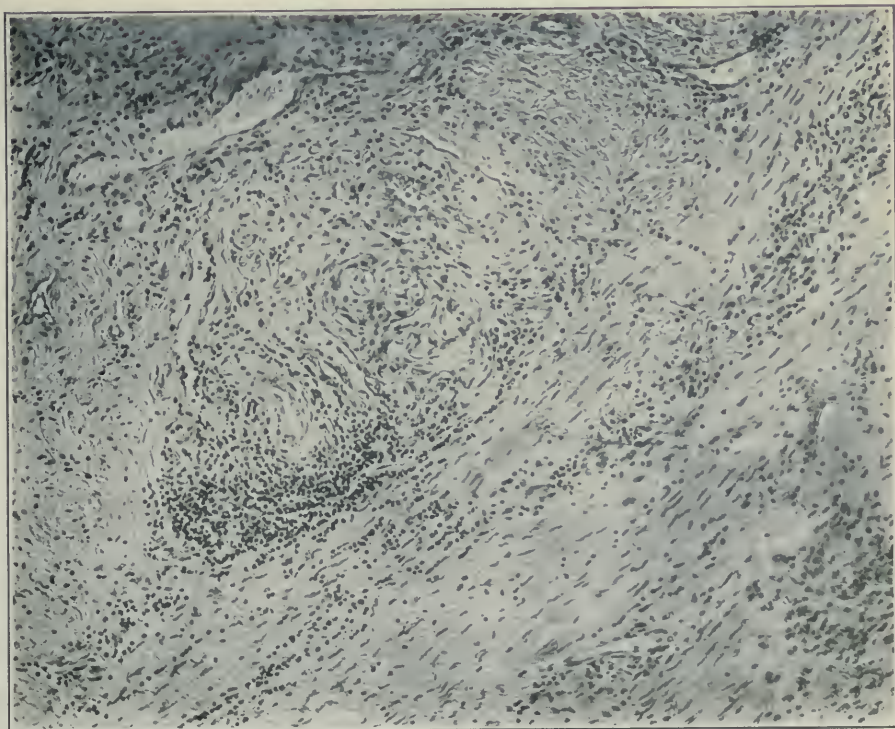


Fig. 8.—Chancre of cervix. Outer zone of cervical wall. Smaller perivascular infiltrations.



eral small myofibromas of the size of large peas. The wall was thick, and firm, the endometrium presented no changes to the naked-eye inspection.

*Microscopical Appearances.*—Sections from the cervix showed a loss of the surface epithelium over the greater part of the induration. The surface of the ulcer or erosion rather, presented little or no exudate, and no diphtheritic membrane, consisting only of the denuded tissue somewhat more condensed and deeper-staining, as if from slight drying or evaporation. Very few polymorphonuclear leucocytes were found in this surface layer. The superficial portion of the cervical tissue presented a zone about 1 cm. in breadth of a dense infiltration as shown in Fig. 1. This infiltration consisted almost entirely of mononuclear cells, mostly of a large lymphocyte or plasma-cell type, arranged in rows or cords throughout the tissue-spaces, or concentrically around the blood vessels and lymphatics. The endothelium everywhere was swollen, the nuclei hyperchromatic, and many mitotic figures were present in these cells. Very few leucocytes were present and no eosinophiles. The whole picture was absolutely characteristic and striking. *The cellular infiltration was developed in situ by mitotic division of endothelial cells, particularly those of the lymphatics and terminal capillaries.* There was no increase of white cells in the blood stream, and no evidences of cellular exudation from the vessels into the tissues. This local formation of the cells constituting the infiltration of the chancre is seen better in the case of cervical chancre than in any other chancres we have studied. The histologic structural arrangement of elastic tissue, voluntary muscle bundles and blood vessels gives to the developing syphilitic lesion of the cervix a more precise structural outline than is the case in chancres of the external genitalia, lips or mouth.

Fig. 2 shows the next deeper zone passing in from the surface. In this area, which is more vascular, with a greater capillary development the cellular infiltration seems more marked and the endothelial proliferation greater. In this zone angioblastic budding and sprouting is evident, and based upon our experience in the study of other chancres we estimated the age of the lesion to be about that of four to six weeks. The patient could not have developed the syphilis during the six days she was in the hospital before



the operation but had a primary lesion of the cervix several weeks old when she entered. Her negative Wassermann reactions at this time are in harmony with this stage of the infection. In this second zone the origin of the lymphocyte and plasma-cell infiltration by mitotic division of the tissue endothelium is even more clearly evident than in Fig. 1. The lymphatics and lymph spaces show a more marked proliferation than does the endothelium of the capillaries. The infiltration is wholly histiogenetic in origin.

In Fig. 3 the next deeper zone is shown, that of medium-sized arterioles and veins. The histology, therefore, presents a more striking perivascular arrangement, the vessels being concentrically thickened as the result of the cords of mononuclear cells of the lymphocyte or plasma cell type packing the perivascular lymph spaces. Between these larger concentrically thickened vessels there is a more dense infiltration resulting from the endothelial hypertrophy and proliferation in the smallest capillaries and lymphatics, particularly in the latter. The compressed lumen-like arrangement of these cells is very clearly shown in the photomicrograph. Such a histologic picture, as presented in Fig. 3 is absolutely characteristic of syphilis outside of certain exceptional conditions in the central nervous system.

Fig. 4 shows the appearances of the next zone still going in from the surface of the cervix. Larger and thicker-walled arterioles and characteristic cleft-like veins give a greater prominence to the vessels themselves. The thicker intima of these vessels shows less involvement, the infiltrations being more marked in the smaller capillaries and lymphatics between the larger vessels. Fig. 5 is a higher power view of one of these medium-sized arterioles shown in Fig. 4. The transformation of the spindle cells lining the perivascular lymph spaces into large oval or round cells with hypertrophic or dividing nuclei with the resultant formation of cords of deeply staining mononuclear cells of lymphocyte or plasma cell type in the perivascular tissue spaces is clearly shown here. Fig. 6 shows a venous space in the same area. The mononuclear cells extend to the intima itself; the vascular endothelium is hypertrophic and shows evidences of proliferation and formation of these cells. In some of the veins the hypertrophy of the endothelium gives a gland-like appearance to the vessel, the endothelial cells appearing less

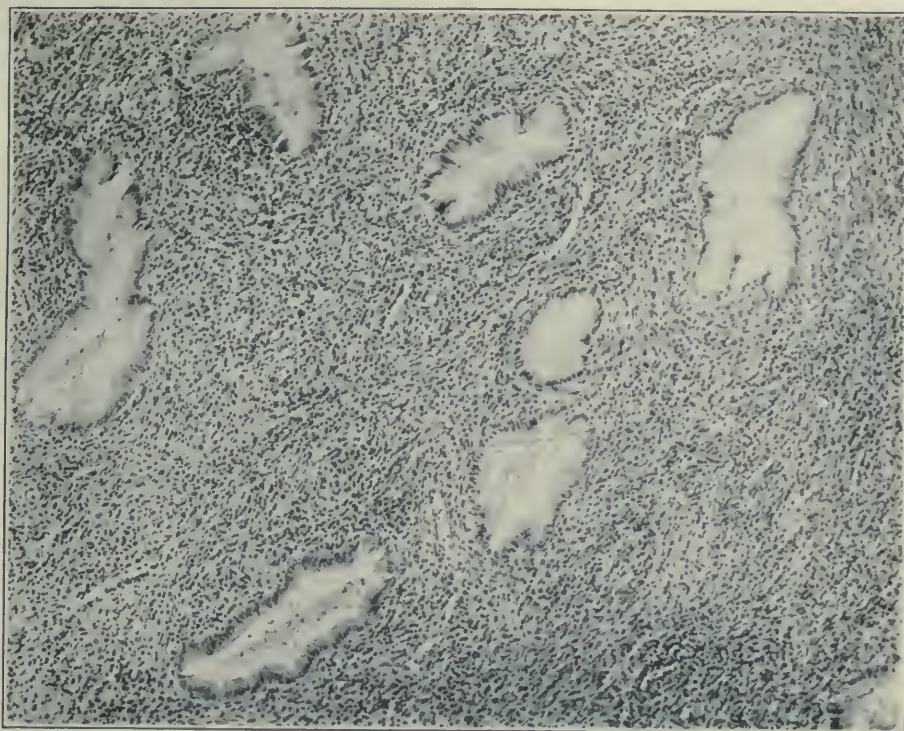


Fig. 9.—Chancre of cervix. Mucosa of cervical canal, showing plasma-cell infiltration of the interstitial tissue.

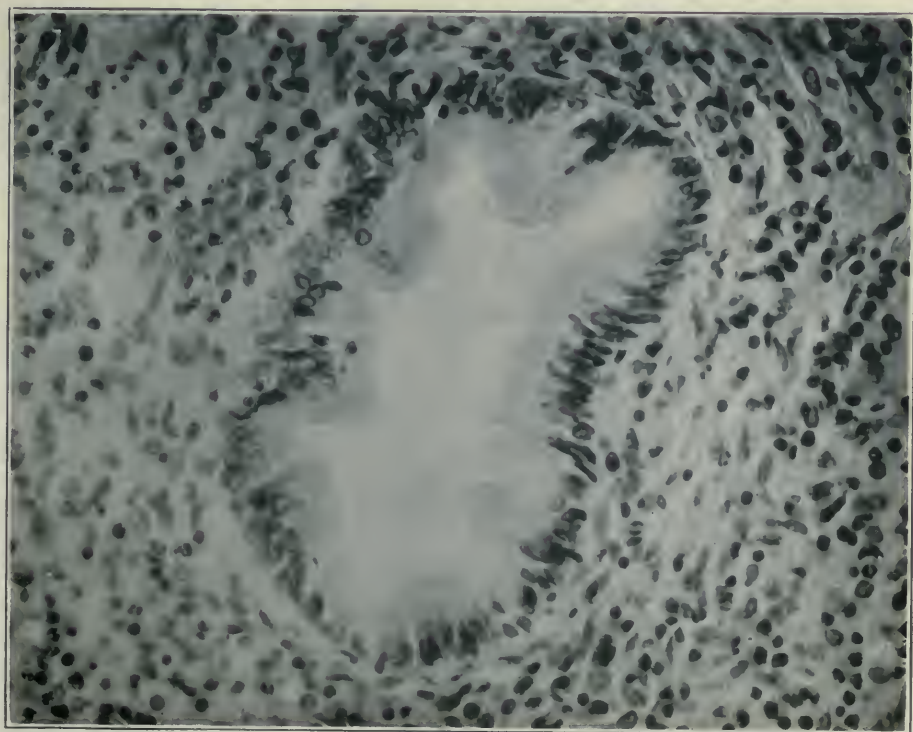


Fig. 10.—Chancre of cervix. High power of cervical gland showing character of periglandular infiltration, with many mitotic figures.





spindle-shaped, more oval or cuboidal, with deeply staining nuclei. Mitotic figures are of common occurrence in the walls of these vessels.

Fig. 7 shows the character of the infiltrations in the musculature of the cervix. It is of the same character, perivascular in the case of the larger blood vessels, and more diffuse in the connective tissue between the muscle bundles, along the smaller capillaries. Because of the fact that the muscle shows little infiltration of the bundles the total infiltration is much less in a given area, but the cellular proliferations extend entirely through the uterine wall into the outer tissue layers, where they occur particularly around the vessels and nerve trunks, as shown in Fig. 8. In the portions of parametrial tissues attached to the specimen similar infiltrations occur.

In the cervical canal the mucosa shows the same changes in the interstitial tissues of the mucosa. The glands are pushed apart and slightly compressed, but their epithelium is apparently unchanged, as is seen in Fig. 9. Because of the richness of this tissue in small capillaries the endothelial proliferation and plasma cell formation are more evenly diffuse. Its essential character is the same as elsewhere. In the high power (Fig. 10), the periglandular tissue shows many hypertrophic endothelial cells, with numerous mitoses, and histiogenetic lymphocytes and plasma cells.

Sections taken from all portions of the uterine wall show that throughout the entire organ the perivascular infiltrations of lymphocytes and plasma cells are present, although to a much less degree than in the cervical portion. Fig. 11 is a section taken from the body of the uterus towards the fundus. It represents the changes seen all through the uterus, in the form of the relatively slight mononuclear infiltrations of the tissue-spaces. The higher power (Fig. 12), shows the cord-like arrangement of these, and their origin from the endothelium of the smallest capillaries, the hypertrophy and increase of the endothelial cells often giving a gland-like appearance to the capillary. The endothelium of the larger vessels shares but little in this proliferation. The diffuse involvement of the uterine wall at this early stage is of especial importance in the general pathology of syphilis.

Sections mounted on cover-glasses and treated by the new silver-

agar method of Warthin and Starry showed typical *Spirochete pallida* in great numbers through these infiltrations and in the smaller capillaries. Because of the contraction of the tissue it was difficult to find any organisms showing their full length in the same focal plane, so that a photomicrograph showing an entire organism could not be made. Figs. 13 and 14 show two magnifications of typical pallida in a small capillary from the middle portion of the cervical wall. In the microscope the entire organism can, of course, be brought into view by focussing. The typical rigid spiral is, however, sufficiently characteristically shown in the photomicrographs.

The histologic picture, with the presence of *Spirochete pallida* in the tissue lesions proved conclusively that this woman had a well-developed primary lesion of the cervix at the time of hysterectomy. There was not the slightest appearance of malignancy either in the cervix or endometrium. The small myofibromatous nodules found showed no malignant change. The diagnosis of primary syphilis of the cervix, of 4 to 6 weeks' duration was, therefore, made by one of us (Warthin). The contention of the patient that she was infected in the hospital, just before the hysterectomy, from the needle used in obtaining blood for the first Wassermann reaction was, therefore, demonstrated conclusively to have no foundation of fact. When discharged from the hospital she had no evidence of cutaneous syphilis and her reaction was negative. When she returned later, December 18, 1920, with a characteristic eruption her Wassermann was strongly positive. On the strength of the pathologic evidence and testimony, in connection with these facts, the jury after two hours' deliberation found no cause for damages.

Because of its medico-legal aspects the case has an especial practical interest, but it has also a broader significance for general practical medicine—and that is the thesis advanced at the beginning of this paper, of the importance of a more certain differential diagnosis between carcinoma and syphilitic lesions of the cervix. In this article we shall consider only the diagnosis of the primary lesion, reserving a study of late cervical lesions for another paper.

From the cases reported in the literature the clinical appearances of chancres of the cervix differ so greatly that no distinctive feature can be taken as affording a basis for a positive naked-eye diagnosis. In size they have been described as varying from a small



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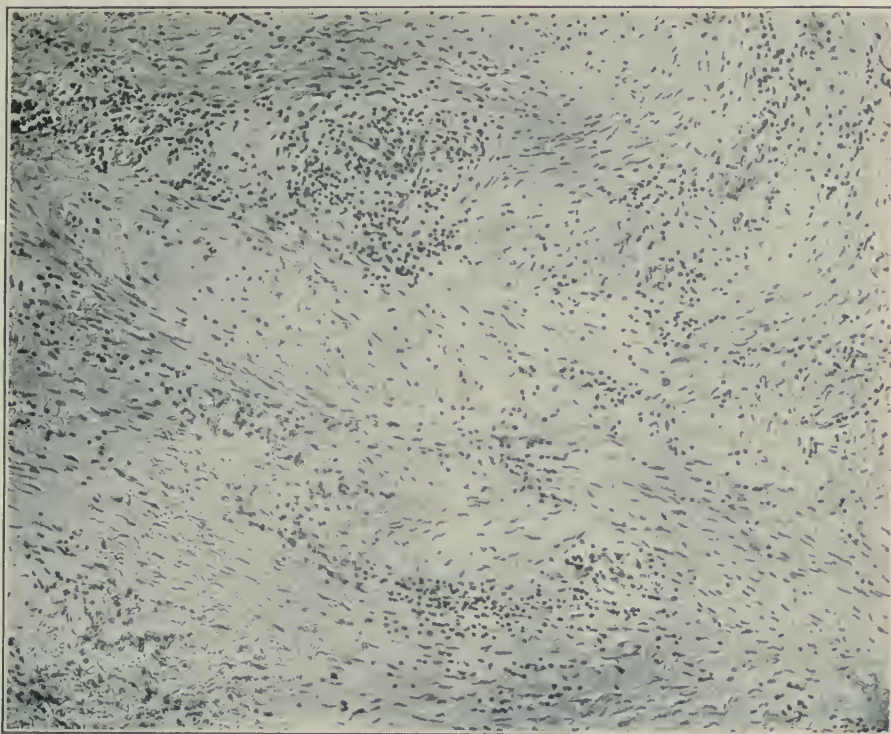


Fig. 11.—Chancre of cervix. Section of myometrium from body of uterus showing smaller plasma-cell collections in the tissue-spaces and along the smaller vessels.

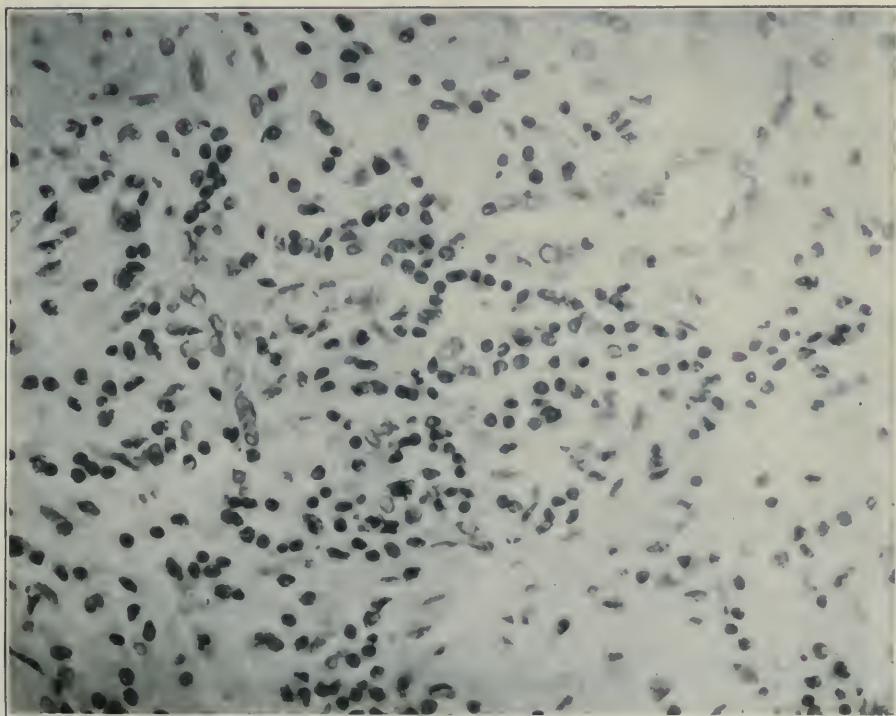


Fig. 12.—Chancre of cervix. High power view of infiltrations in uterine muscle in the body of the uterus. Hypertrophy and proliferation of endothelium of capillaries and lymph spaces with formation of plasma-cells.





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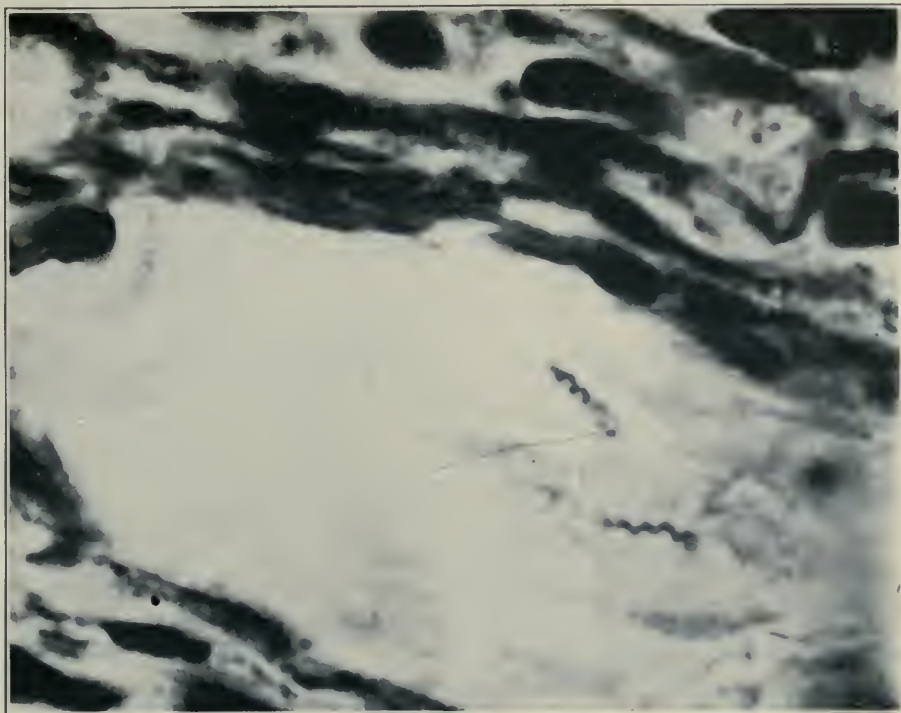


Fig. 13.—Chancre of cervix. Section stained by Warthin and Starry's silver-agar method. Two spirochetes of syphilis, in small capillary, only part of the organisms being in the same focal plane. Dark spots between the tissue-cells are other spirochetes out of focus.

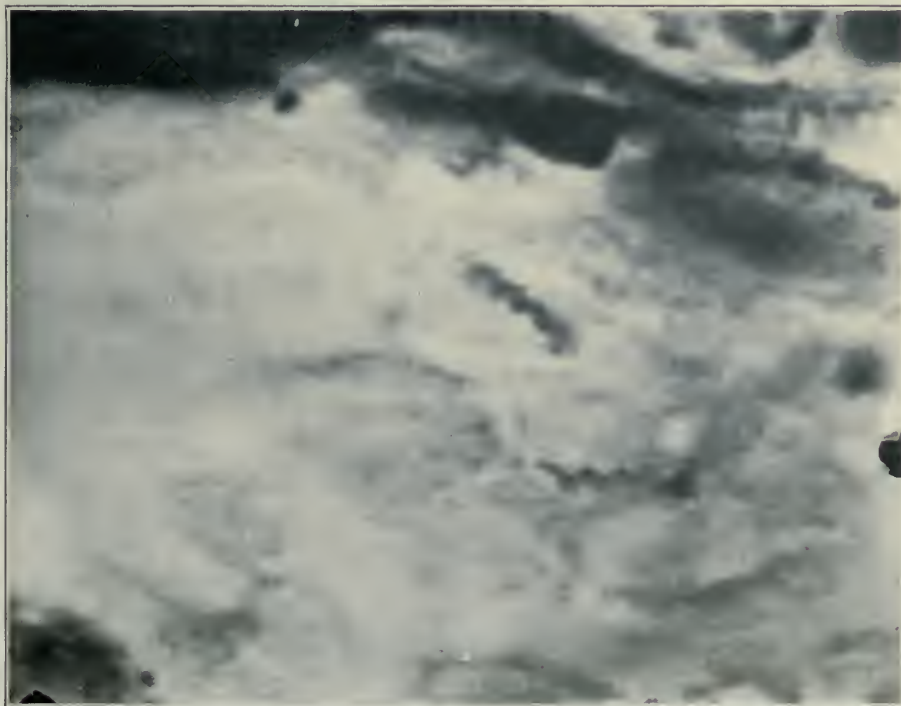


Fig. 14.—Chancre of cervix. Higher power view of preceding.





flat or papular lesion, flat erosion, diphtheritic ulcer, ulcerated sclerosis, gangrenous ulcer, to hypertrophic fungating vegetations involving the whole cervix. The variation in color, consistency, tendency to hemorrhage, etc., is so great that no single characteristic can be regarded as possessing positive diagnostic value. The great divergence in the descriptions given may in part be explained by different stages of development of the lesion. It is very probable, however, that many of the cervical lesions described as primary chancres were in reality not so, since the diagnosis was purely clinical and not controlled by other examination. In the presence of other signs of syphilis elsewhere a cervical lesion of any kind might easily be regarded as the primary without any other grounds than the coincident occurrence of the conditions. It is of interest to note that nearly all of the cases in which chancre of the cervix has been diagnosed have shown well-marked cutaneous lesions of syphilis and the search for the cervical condition has been made only after the diagnosis of syphilis has already been determined. We must agree with Gellhorn and Ehrenfest that the primary cervical chancre offers no truly characteristic and pathognostic features clinically.

We believe that the diagnosis of primary cervical chancre can be made through its characteristic pathologic appearances and by the demonstration of the *Spirochete pallida* in these tissue-lesions. Indeed, in all of the cases of cervical chancre we have seen the histologic appearances are so striking and characteristic that we believe them to be pathognostic in themselves. In our experience the distinctive pathology of the chancre is more clearly shown in those of the cervix than in chancres elsewhere in the body. The demonstration of the spirochete in these lesions only makes this conviction doubly sure. The diagnosis of chancre of the cervix can be made, therefore, only through a microscopic examination of tissue excised from the lesion; and only in this way can the differential diagnosis between carcinoma and syphilis be determined.

It is not sufficient, as has been reported in the literature in a number of cases, to demonstrate the presence of *Spirochete pallida* in smears made from the cervical lesion. A woman may be a syphilitic and still have carcinoma of the cervix. As is well known the syphilitic woman may show spirochetes in her menstrual blood and

genital<sup>1</sup> secretions, even in the absence of all local lesions, and in such a case with carcinoma of the cervix the spirochete might easily be found in smears made from the carcinoma itself. A diagnosis of syphilis alone under such conditions might be disastrous to the patient, and such an event has apparently happened once at least, in the literature.

#### CONCLUSIONS

The diagnosis of chancre of the cervix should be made only on the basis of a histologic examination of tissue excised from the lesion. The histologic picture is pathognostic. The demonstration of *Spirochete pallida* in the characteristic tissue-lesion is a confirmatory procedure.

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## CONCERNING THE PRE-COLUMBIAN EXISTENCE OF SYPHILIS IN EUROPE

BY DOUGLASS W. MONTGOMERY, M.D., SAN FRANCISCO, CAL.

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IT IS said that truth is hidden in the bottem of a well, and besides mankind often takes the trouble to fill up the well with stones. Sometimes these stones are piled in with the intent to deceive, at other times with a careless jollity and disregard of consequences. It was in this latter frame of mind that Rabelais changed the date in a caustic old epitaph written by Marot on a monk, a native of Orleans named Brother John l'Évêque. The original epitaph runs to the effect that:

Here lies and reposes and sleeps the late bishop of Orleans, who died in the year 1520. The immediate cause of his passing was "*la vérole*," (syphilis). The epitaph goes on to state that it would be fine if, on arriving in his celestial abode, he could obtain a room to himself, "*quelque chambre à part*." The good father's trouble, therefore, evidently would interfere with his being a pleasant rooming companion.

In crowded habitations, such as those in heaven must be, the nature of the bishop's trouble would be a matter of moment. Erasmus, a contemporary, who suffered from stone in the bladder, and who was of a most sociable disposition, thanked God that his malady was troublesome to himself alone, and neither fulsome nor disgusting to his neighbors.

In this whimsical epitaph the line in question runs:

*Qui feust l' an mil cinq cent et vingt.*

The old French word "*feust*" is a contraction of the Latin "*defunctus fuit*," was defunct, and the translation of the line would read:

Who died in the year one thousand five hundred and twenty.

Rabelais changed this line to read that he died:

*Et fut l' an mil quatre cens vingt,*

*De la verole qui lui vint.*



Of which the translation is:

And it was the year one thousand four hundred and twenty that he died.

He, therefore, changed the five hundred to four hundred. This would make it appear that the frail churchman departed this life seventy-two years before the discovery of America. This statement was made by Rabelais, who was not alone the greatest literary man of his day but an acknowledgedly successful physician, and one who took a great interest in syphilis. Admitting this statement to be true, the idea of the Columbian introduction of syphilis from America into Europe could not hold. Esmangart and Johanneau, however, have shown, as indicated above, that Rabelais changed the figures in an epitaph written by Marot, in order more readily to fit into his verse, and without any regard whatever for their historical accuracy.

The above is only one example of many of the statements made in regard to the pre-Columbian existence of syphilis in Europe. The arguments, however, both general and particular, in favor of the American origin of syphilis are, to my mind, altogether too strong to be explained away by individual historical assertions, which are so liable to error.

## A THOROUGH HISTORY AN IMPORTANT FACTOR IN SYPHILIS

BY C. J. BROEMAN, M.D., CINCINNATI, OHIO

*Assistant Director, Department of Dermatology and Syphilis, Cincinnati General Hospital, Medical Department, University of Cincinnati*

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IN ORDER to appreciate how completely the medical profession's entire conception of syphilis has been revolutionized in the last twenty years, one has only to examine any authoritative work on this subject which came out at the beginning of this century. Take for instance, the *Symposium* published by E. B. Treat & Co. in 1902. This consists of some twenty-five contributions by distinguished specialists of that day, and can be regarded as a very just summary of the most advanced practice then prevalent. Many of the authors there represented, are still practicing and writing, their experience covering the period of tremendous advance which has been coincident with the twentieth century.

In examining the recommendations of these men one is impressed by the importance which every one attaches to a complete and accurate antecedent personal history. And it is also noticeable that the majority have some remarks to make concerning the exceptional difficulty of obtaining such a history from syphilitic patients. Because of the lay attitude towards syphilis, and its apparently inextricable entanglement with moral and ethical considerations, the physician was debarred from bluntly demanding the exact dates of possible exposure and a consecutive account of the patient's movements and associations in relation to it, or even from making inquiries as to the likelihood of dissemination of the disease by the patient himself, since the onset of his infection.

It is not strange, therefore, as soon as the medical profession was furnished with what appeared to be a reliable means of determining whether or not an individual had syphilis, without resorting to the delicate and nerve-straining task of coaxing him into confessing—for it was just that—exposure to infection, that every medical man

hastened to avail himself of it. So the past twenty years has seen less and less attention given to obtaining a syphilitic history, and more and more absolute reliance upon laboratory findings as a means to diagnosis.

Bordet's discovery of hemolysis was given to the world in 1898, but eight years passed before the publication of his paper written in conjunction with Gengou, describing complement fixation, upon which the so-called "Wassermann test" is based. Schaudinn and Hoffmann had already shown that syphilis is due to *Treponema pallidum*, present in the tissues of certain organs, and Wassermann first used the complement-fixation test with such organs in syphilitic monkeys and in 1906 the reaction was applied to man with triumphant success. From that day until now the very name Wassermann has held a magic potency for every one—physician and layman alike—who has to do with syphilis in any of its multitudinous forms and relations. The field of syphilology at once swarmed with eager workers; advance was rapid and all ancient methods of diagnosis and treatment were consigned to oblivion.

It was no longer considered necessary to spend hours, days even, in painful cross-examination to obtain "histories" from diffident and unwilling patients, or careful and long-continued clinical observation before arriving at a diagnosis. All that was needed was to apply "the Wassermann," and—for good or ill—the patient's fate was sealed.

Before long, however, the more thoughtful and conscientious began to realize that the Wassermann reaction, like other human agencies, was not wholly free from possibility of error. It was observed that it was occasionally negative in cases where the signs of syphilis were patent to all observers, and the natural inference was immediately drawn that the reaction might vary under exceptional conditions—be positive when no syphilitic infection was actually present. That these drawbacks to the exclusive use of the Wassermann reaction as a means of diagnosis represent facts which must be accepted and dealt with, and not merely academic possibilities, has been over and over again demonstrated in my own practice, and doubtless in that of every other man who is called upon to give treatment for syphilis.

Last year a young woman was referred to me for treatment of a



skin eruption which had been diagnosed as of syphilitic origin. She had previously been in the hands of a very competent serologist, by whom the diagnosis had been made. Repeated Wassermann tests had yielded a consistently negative reaction, but the history had been hurriedly and carelessly taken, so that probably—because of misunderstanding on the part of the patient—the man who had treated her, believed that she had admitted a previous luetic exposure. A thorough examination into the patient's history, together with physical findings, soon convinced me that her trouble was just what it appeared to be—a typical case of pityriasis rosea—and that no syphilis was present.

In his letter concerning this patient the previous attendant wrote that he had obtained a positive history of syphilis, which to his mind explained the presence of the squamous eruption upon the flexor surfaces. He was also of the opinion that there was some spinal cord lesion as the young woman had complained of difficulty in voiding the urine, but there was nothing abnormal about the pupillary reflexes, although those of the knee were absent.

The Wassermann in this case was negative, but cases where all chance of syphilis could be positively excluded have persisted in returning a positive Wassermann. Of such a case Pusey says: "The Wassermann is all right, but it should be appreciated that it is open to error in manipulation. It is not final and unimpeachable evidence, and in improbable cases, a positive reaction should not be accepted as final, unless one can be perfectly sure of the reliability of the process by which it has been obtained. The Wassermann reaction is but one fact in the diagnosis of syphilis. It should be confirmed by other diagnostic evidence."

The Wassermann reaction is still far from infallible, yet where there are no visible lesions it is the most reliable test we have. A positive result is worth more than a negative one. As a rule it is not until fifteen to seventeen days after a chancre appears that the blood-serum reaction is positive. Medication, such as a dose of chloral hydrate, or recent ether or chloroform anesthesia, may cause the serum to give a positive reaction when absolutely no syphilis is present.

The Wassermann is by no means infallible, and its findings must be carefully checked by comparison with all the other diagnostic

data we can possibly muster. There remain the physical examination and the history, and during the past year or two there has been a gradual but none the less perceptible return to dependence upon these two diagnostic aids, which served so well such men as Fournier and Jonathan Hutchinson long before laboratory diagnosis was even dreamed of.

It is one thing, however, to emphasize the importance of a "complete history," and it is quite another to elicit one. History-taking is an art itself, and like most other arts is practiced by many tyros, but very few experts. This is true enough in dispensary syphilis work, but in private practice it becomes a thousand times more difficult. Yet there is no condition we are called upon to treat where an accurate detailed history is of so much importance as in the management of syphilis. It is imperative, therefore, that the successful history taker must bring to bear all the tact and skill of which he is capable, and that he should combine the acuteness of a prosecuting attorney with the adroitness of a diplomat.

Secondary syphilis is usually easy of diagnosis. The physical examination will reveal the remains of a chancre, or an evident rash; there will be lesions of the mouth and throat; adenopathy, or perhaps a patchy alopecia, and the patient will readily volunteer information concerning previous headache or bone or joint pains. It is the early or late conditions which give the most trouble to the diagnostician, and, of course, it is when these stages present themselves that an exact diagnosis is of the most serious importance.

Charles Lyman Greene in his twelve-hundred-page treatise on *Medical Diagnosis* dismisses the history of hereditary syphilis in three lines. "In relation to family history direct inquiry is usually impossible and the physician must ordinarily depend upon the disclosures of parents or the recognition of inherited syphilis in the patient." Despite such discouragement, however, it behooves us to make every effort to bring out the existence of any hereditary or family infection. The majority of these patients are much more willing to discuss the possible misfortunes and transgressions of their forebears and families than to talk about their own, the usual difficulty being for the listener to separate the chaff from the grain, so abundant is the harvest he is sure to reap. Extragenital infection occurs far too often to make it safe to omit a careful consid-

eration of all the patient's housemates, and a study of their occupations, amusements and tendencies may very often transillumine a diagnostic problem of apparently hopeless opacity. There is probably nothing on earth more tedious than the conversational rambling of certain patients, or more exasperating to the nerves and temper of the busy doctor who is trying to elicit a history, but in syphilis, more than any other disease, we can often get our best information when the patient is "off his guard." This is especially true where women are concerned.

Therefore let the patient "talk." Guide him tactfully from the bolt of lightning which made an end of his great-grandfather, to the pneumonia which cut short the career of his father and the cerebrospinal meningitis which blighted the infant years of his little brother James, until he is naturally led to narrate his own physical history. No matter how opposed he may be to the doctrines of Freud and his followers, it is here that we will do well to take a leaf from his book. If we boldly demand to know whether or not there has been a syphilitic infection we will be met, nine times out of ten, by an indignant denial, but a judicious "beating about the bush," will usually bring the questioned one to a point where he realizes that his bridges have all been burned behind him, and admission is not so difficult when it is inevitable.

Four years ago a young man of twenty-three who had previously been under my care presented himself with unmistakable signs of syphilis. After much patience and exhaustive—even *exhausting* questioning—I succeeded in learning the probable source of infection, and to persuade him to bring in the suspected person for examination. This was a girl of eighteen years of age, and her history disclosed that she had been infected for two years without any knowledge of the fact. Her serum gave a four-plus Wassermann, and physical examination revealed the presence of a syphilitic gastric ulcer. One month of intensive treatment cleared up all her symptoms. The Wassermann was extremely valuable in this instance, but without the history of both patients it would have been useless because it would have never been applied.

During and since the war so much propaganda in regard to syphilis has been spread abroad that the laity are vastly better acquainted with its signs and manifestations, its mode of infection



and clinical course, than was the case five years ago. For this reason a patient who has knowingly exposed himself to syphilis and is desirous of concealing the fact is usually better able to resist the conversational pitfalls laid for him by the wily examiner. This again is peculiarly true where women are concerned.

Bulkley in 1894 reckoned that 50 per cent of the women who had syphilis had acquired it innocently, and has since reiterated his statement. It is likely that the remaining 50 per cent who have acquired it through illicit sexual intercourse will be pretty well "up" on the clinical manifestations, and that a fair proportion of them may be extremely anxious to conceal any part of the history which might have a direct bearing upon their present illness. Here then the physician's utmost tact will be required. He must be cautious, but at the same time straightforward, and his attitude must be most of all, one of absolute scientific detachment. This attitude is well brought out by Stokes in his popular book *The Third Great Plague*. Though this is designed for lay reading, the physician may glean some useful hints from a perusal of its pages. As he puts it, "It is the unpretentious spirit of talking about a spade as a spade and not as 'an agricultural implement for the trituration of the soil' that we should take stock of the situation and of the resources we can muster to meet it."

The importance of exact diagnosis should be impressed on the patient, and the impossibility of obtaining it except through a full knowledge of all antecedent possibilities be especially emphasized. One can be seriously impressive without being terrifying. If the patient is convinced of the physician's sincerity, and impartial scientific attitude, he, or still more often, she, will usually find it a relief to become extremely minute and explicit. When the ideas of social stigma, and moral turpitude can be divorced from the questions of exposure and infection, the history will be much more spontaneous and detailed. It is not an easy matter to put things in this light, but it can be done, and the value of such a history needs no pointing out.

Some patients will be more communicative if they can be led to believe that the examiner already possesses full information as to their condition and is only seeking corroboration, but the majority will talk more freely if they are convinced that upon their frank-

ness depends the chances of relief and permanent cure. Even a very ignorant person once assured that he has syphilis will usually be sufficiently alarmed to be willing to cooperate with his physician as much as he can. To bring him to that state of mind is the task of the skillful gatherer of case statistics.

A good personal history should include definite family and social data, sufficient to enable the physician to judge the possibilities of hereditary taint, conjugal or other family and household sources of infection; it should give details of the patient's childhood ailments, activities and associations; and it should incorporate minute details of recent contacts, physical and psychic alike, which may in any way lead to detection of a definite exposure. Schamberg's "epidemic" of lip chancre, where eight innocent persons were infected from a single source of playing "kissing games" at a social gathering, has become a classic "dreadful example," but it may very well serve both as a reminder to the physician himself, and as a conversational crowbar for prying loose the outer bulwarks of a patient's reticence. It is well to bear in mind that giving the opportunity to consider the possibilities of extragenital infection may very well lead to admissions which will eventually disclose the exact manner in which the disease was actually contracted.

The compilation of such a history will be a tedious matter for both physician and patient, but it will abundantly repay the trouble. After all it is not that so many medical men are incapable of getting full histories from patients suspected of syphilis, but rather that so many are too bashful or lazy or indifferent to make the effort and take the time to obtain them. "The Wassermann is all right," it is our chief aid to diagnosis, but it must be supplemented by a most thorough physical examination. The physical findings are highly important, but their value is increased a hundred-fold when the data thus obtained can be accurately checked up against a full personal and clinical history. Therefore, give heed to the history, and never be prevented from getting it by false modesty or laziness, or a fear that the patient will be "offended" and perhaps seek the service of some "less curious" medical adviser. Use your best skill and the utmost tact you can muster in bringing out the facts. Do not vary from the impersonal scientific attitude. But, if despite this, the patient's sensibilities are outraged and he refuses the necessary

information, then apply to your own case Dogberry's advice to the watch:

"Take no note of him but let him go; and presently call the rest of the watch together, and thank God that you are rid of a knave."

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# SYPHILIS OF THE GENITAL ORGANS OF THE MALE AND THE URINARY ORGANS, V.\*

PENIS, URETHRA, URETER, KIDNEY PELVIS

BY LOYD THOMPSON, M.D., HOT SPRINGS NATIONAL PARK, ARK.

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ALMOST from the earliest knowledge of syphilis it was recognized as a disease contracted largely through venery, in fact for a long time, except for certain bizarre theories of etiology which were at times given credence, this method of transmission was the only one observed. It is therefore obvious that lesions of the penis, particularly the chancre, should have been recognized from the earliest times.

## CHANCRE

*Development.*—The term chancre is a French word derived from the Latin *cancer*. This lesion usually begins as a small reddish spot at the site of inoculation and soon develops into a papule. It may or may not at this time convey to the palpating fingers a sense of resistance. The surface may be moist with a light sticky, clear, sanious fluid or it may be perfectly dry. The attention of the individual may first have been called to it by itching or it may have been observed by him as what is vulgarly known as a "hair cut." The lesion is generally nearly circular in outline and of a dark red color, which later changes to gray. It varies greatly in size, sometimes being so small as to pass unnoticed, and again it may be 4 to 5 cm. or over in diameter. While this lesion of syphilis is usually single, it may be multiple. It would seem that the number usually depends upon the number of abrasions which exist at the time of inoculation, but multiple chancres may occur by autoinoculation.

\*This is the fifth and last of a series of articles dealing with syphilis of the genital organs of the male and the urinary organs. The first four articles of the series appeared as follows:

Syphilis of the Bladder. *Am. Jour. Syph.*, January, 1920, iv, 50. Syphilis of the Kidney. *Jour. Am. Med. Assn.*, July 3, 1920, lxxv, 17. Syphilis of the Prostate. *Am. Jour. Syph.*, July, 1920, iv, 323. Syphilis of the Scrotum, Testicle, Epididymis, Spermatic Cord, and Seminal Vesicles. *Ibid.* October, 1920, iv, 706.

Reprints of the entire series bound together may be obtained from the author.

In a few days a hard mass or induration develops in the vast majority of cases at the base of the chancre. This varies greatly in size and shape. It may be so slight as to be undetected except by the most skilful palpation, or it may be hard and nodular, being readily recognized on sight. At times it is thin and lamellar, resembling a piece of parchment or it may be of annular shape, forming a ring around the sore. The induration is not inflammation, as it takes place without the cardinal symptoms of that pathological process. It varies greatly with the location of the chancre. If the latter is in a spot where the tissues are firm and resistant, it is much more difficult of detection. Generally speaking, when the chancre is located on the mucous membrane of the penis the induration may be felt more easily than when the skin is the seat of the infection. The induration usually lasts after the sore is healed. The sore itself generally heals even without treatment and leaves little or no trace of its existence. This is probably due to a local acquired immunity which causes the *Spirochete pallida* to die out in the sore. However, a pigmented spot may persist for some time and occasionally there may be a white spot left, due to loss of tissue, which may last for years.

*Location.*—The most frequent location of the chancre of the penis is the *balano-preputial* fold. This is also the most frequent location of all chancres and is undoubtedly due to the fact that in this location slight abrasions most frequently occur. The location, which next to the above, is most often affected is the *lining mucous membrane of the prepuce*. A chancre of this location often cannot be observed, owing to the presence of a phimosis, which may or may not be due to the lesion itself. In such a case circumcision should be performed to permit of an accurate diagnosis. The *preputial orifice* is the next most frequently attacked by the syphilitic organism, and in this location the sore gives to the prepuce the appearance of having been split. At first the split or splits look like mere scratches which later become indurated and the prepuce thickened. Often the chancre may surround the entire cutaneous border assuming a crown-like appearance with marked phimosis.

The order of frequency of other chancres of the penis is as follows: *frenum, skin of penis, glans penis, and urinary meatus*.

A chancre of the *skin of the penis* begins as a small abrasion which

gradually spreads until it may attain a diameter of 2 or 3 cm. The edges are hard and the induration is thin, parchment-like and quite easily detected by palpation.

When the surface of the *glans penis* is the seat of a chancre it begins as a flat erythematous spot, which in a short time becomes depressed in the center with hard, indurated edges.

Either one or both lips of the *urinary meatus* may be inoculated with the *Spirochete pallidum* and a chancre result. However, that both are affected is the rule. Induration is invariably present, though slight. A scanty, viscid, discharge is found which generally glues the lips together. There is usually some impediment to the flow of urine, which, however, disappears when the lesion heals.

*Varieties.*—It will be seen from the above that chancre of the penis does not exist as a typical pathologic lesion. There are, however, a number of fairly constant varieties which, to a large extent, depend upon their location.

The first is the *indurated papule*. This lesion begins as a slight, dark red elevation which may attain the size of 2 cm. or more in diameter. It is dry and hard and the surface is not broken throughout the entire course of the lesion.

The *eroded chancre* is probably the most frequent form of this sore. It has the appearance of a rounded or oval spot with a smooth, raw surface. The edges are not elevated above the surrounding tissue, and while the center is usually concave, it may be convex or dome-shaped. Such a chancre may be as small as a split pea or as large as a five-cent piece in diameter.

Quite frequently a chancre assumes the form of an *ulcerating sore* which may involve only the superficial layers or may burrow deep into the tissues. Such a lesion has been termed a *Hunterian chancre*. Induration is usually quite marked in the beginning, but may become lessened as the lesion grows older. It may be covered with a grayish false membrane, and a slight, thin, sanious exudate is present.

Occasionally in the beginning a chancre has the appearance of the mark left after the application of a stick of silver nitrate. This type of lesion has been called the *silvery spot*. It gradually assumes a dark yellow color and considerable induration exists.

A *recurring or relapsing chancre* (*chancre redux*) is a lesion, prob-



ably a gumma, which has all the appearance of an original chancre and which develops on or near the site of a previous chancre. It may occur at any time, from a few weeks to ten or twelve years or longer after the healing of the first sore. The surface usually remains intact but it may become eroded.

*Complications of Chancres.*—A chancre may be modified in appearance and course by inflammation, complication with chancreoid or by phagedena.

*Inflammation* of the chancre may be due to the application of caustics or to the presence of pyogenic organisms. In either case the appearance of the lesion will be modified greatly. The sore and adjacent tissues become red and swollen, while pain, which is rare in uncomplicated chancre, may be most intense.

The complication of a chancre with *chancreoid*, which is known as a *mixed sore*, is not infrequent. The double infection may occur at the same time from the same source or the chancre may be subsequently inoculated with the bacillus of Ducrey, the causative agent of chancreoid. In the former case the typical chancreoid ulcer, which develops first, owing to the shorter incubation period, is gradually surrounded with the induration of the syphilitic lesion. While if the chancre is later infected with the chancreoid bacillus, the induration is destroyed by ulceration.

The most serious complication of chancre is *phagedena*, which fortunately, is rather rare. This condition may develop in a chancre at the beginning or it may not appear until quite late. It is probably caused by the organism of Vincent's angina and a mixed infection of pyogenic bacteria, although any lowering of the vitality, such as that resulting from drunkenness, diabetes, nephritis, etc., may predispose the individual to it. The ulcerative process usually spreads on all sides and deep into the tissues, although it may progress in only one direction (serpiginous ulceration). The sore is irregular with markedly congested and edematous edges. It bleeds easily and may even erode through a vessel of some size, causing considerable hemorrhage. There may be sloughing and loss of tissue.

*Diagnosis.*—The diagnosis of chancre of all the manifestations of syphilis is without doubt of the most importance. This is true, because in the vast majority of cases if diagnosed while the chancre

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Fig. 1.—Small chancre of glans. (Silvery spot.)





is the only lesion present, the successful outcome of the treatment may be assured.

The presumptive diagnosis of chancre of the penis can probably be made in the majority of cases by the history, if this can be obtained, by the general appearance and by the induration, but I am decidedly of the opinion that a definite diagnosis of syphilitic chancre without further clinical evidence is seldom, if ever, justifiable without the finding of the *Spirochete pallidum* or a positive Wassermann test.

The most important condition to be differentiated from chancre is *chancroid*.

The following table shows the main points of differentiation:

CHANCRE	CHANCROID
1. Incubation three to four weeks, rarely under ten days.	1. Short. Usually under five days.
2. Papule, erosion or ulcer with sloping edges.	2. Pustule or ulcer with sharply cut edges.
3. Usually single.	3. Usually multiple.
4. Scanty serosanguineous discharge.	4. Abundant purulent discharge.
5. Indurated base.	5. Soft or inflammatory base.
6. <i>Spirochete pallidum</i> .	6. Bacillus of Ducrey.
7. Wassermann positive or negative.	7. Always negative.
8. Bilateral inguinal adenitis.	8. Unilateral inguinal adenitis.

It must be remembered that chancre and chancroid are very frequently associated in the so-called mixed sore which will render the diagnosis less certain owing to the greater difficulty of demonstrating the organisms of syphilis. It is my custom with all cases diagnosed chancroid by the finding of the bacillus of Ducrey and the failure to find the *Spirochete pallidum* to make Wassermann tests quite frequently, at least every two or three days, for several weeks, until all danger of a concomitant syphilitic infection is past.

*Chancre* must be differentiated from *simple erosion*, and this can usually be done by the absence of induration and adenitis in the latter condition as well as by the failure to find spirochetes.

*Herpes* may sometimes be mistaken for chancre, but in the majority of cases the multiplicity of the lesions, or if single they are made up of numerous small intersecting segments of circles, the presence of burning and itching, the usual absence of induration and adenitis, and the absence of spirochetes, will serve to diagnose the condition.

Occasionally the ulcerated or papular lesion of *scabies* may be mistaken for chancre. As with herpes, there is usually little or no induration and adenitis, and, of course, the organism of syphilis is never found, while other evidences of scabies will be present.

*Gummas* sometimes very closely resemble chancre and constitute, at least in most instances, the so-called *chancre redux*. They are to be differentiated from true chancre by the history, that is with gummas, a history of syphilis, and with chancre a history of exposure, and by the typical adenitis seen with chancre and almost always absent with gumma. Spirochetes may be found in both conditions, although more abundantly in the chancre. The Wassermann test may be positive or negative in either.

*Prognosis.*—That syphilis may sometimes be aborted when no other symptoms but chancre exist by the institution of energetic specific treatment is in my opinion, undoubted. The first essential, however, must be a correct diagnosis, that is, the finding of the *Spirochete pallidum* in the secretion from the chancre. Following this specific medication should begin at once. However, aside from the specific treatment which must be resorted to in all cases of syphilis, and which is not within the scope of this paper to discuss in detail there are certain local measures which are of more or less value.

Numerous syphilographers have advocated the so-called abortion of syphilis by cauterizing or excising the chancre. Hunter<sup>1</sup> probably was the first to undertake these procedures, but did not consider them as absolutely certain preventatives of constitutional syphilis, although he did think that in a large percentage of cases they were successful. However, in the light of modern knowledge of the infecting organism such procedures undoubtedly do not abort the disease. Formerly I did not consider this method of procedure advisable, but recently I have changed my views on the subject and recommend the excision of the chancre where such a procedure is possible without too much destruction of tissue. In this manner certainly one focus of spirochetes is eliminated.

Numerous caustics for the destruction of chancres have been advocated. One of the best of these in my experience is the one proposed by Bansbach<sup>2</sup> which consists of calomel 10 parts, zinc sulphate

10 parts, and chlorine water 50 parts. This is applied on a piece of cotton, covered with oiled silk, and left in place twenty-four hours.

The local treatment of chancre of the penis unless excision or cauterization is resorted to, is, as a rule, extremely simple, consisting, in uncomplicated chancres, of washing three or four times a day with warm boric acid solution, weak bichloride solution (1 to 5000) or potassium permanganate solution (1 to 4000). Following this the lesion should be dusted with thymol iodide or some similar dusting powder, and covered with a piece of sterile gauze. When healing begins, or if crusts form, calomel ointment (10 per cent) or hectine (20 per cent) should be applied.

Chancre complicated by chancroid, the so-called mixed sore, should be treated as if the syphilitic infection did not exist, that is some form of cautery should be employed. I have found the following procedure very satisfactory: The parts are first thoroughly cleansed with warm water and dried, after which the lesions are "ringed" with vaseline. Cocain crystals are next applied to the sore and removed with sterile water after remaining in contact two or three minutes. Pure carbolic acid is next applied with a cotton pledget on an applicator and after remaining a minute or two pure nitric acid is applied by means of a glass rod and allowed to remain in contact two or three minutes when the excess is removed with a pledget of cotton and a dry dressing of thymol iodide applied.

Phagedenic chancre should be treated by cautery with chromic acid, or the actual cautery. In the majority of cases general anesthesia is necessary, as the cauterization must be thorough to be effective. Following the cautery the lesion should be dressed with an antiseptic solution and when the slough which forms is removed dusting powders such as thymol iodide or iodoform may be applied.

#### SYPHILODERMATA

The penis is occasionally the seat of the various types of syphilodermata. Fig. 4 is from a photograph of the miliary papular syphiloderm and these lesions were practically the only ones present in this case.

Gummas of the skin or mucous membrane of the penis are more frequent than the other types of lesions, and as pointed out above constitute, in most cases at least, the so-called *chancre redux*. They



do not differ from gummas of the skin and mucous membrane of other regions. They must be differentiated from chancre and the diagnostic points have been given under chancre.

#### CORPORA CAVERNOSA

Syphilis occasionally attacks the corpora cavernosa in the form of gummas. These lesions vary in size from a pea to a small marble, are painless and of insidious development. As a rule they are located near the extremity.

They may pass entirely unnoticed until they attain a size sufficient to interfere with erection, that is there is a bending of the organ, usually laterally but sometimes up and down, according to their location.

Usually they do not soften and break down as most gummas do, which has led some authors, notably Fournier,<sup>3</sup> to be sceptical as to their syphilitic nature. However, there seems to be no doubt that they do occur. The following case came under my personal observation:

F. H., male, aged twenty-five, negro, soldier. Family and past history so garbled as to be of little or no value. Admitted several attacks of gonorrhea and several venereal sores. Complained of "knots" in penis and a lateral curvature upon erection. Examination revealed a scar on the balano-preputial fold and two hard nodules one the size of a pea, the other somewhat larger in the left side of the penis about an inch and a half from the extremity. A diagnosis of probable gumma was made and as the Wassermann was 4-plus he was placed upon antiluetic treatment. Arsphenamine 0.6 gram and mercury salicylate 1 gr. were administered at weekly intervals, while potassium iodide was prescribed in 10 gr. doses t.i.d. increasing 5 grs. a day. In three weeks the nodules had entirely disappeared.

Gummas of the corpora cavernosa must be differentiated from chronic circumscribed inflammation and this can usually be accomplished by the history and the presence or absence of other evidences of syphilis including the Wassermann test. If, however, there is some doubt the therapeutic test might be applied.

#### URETHRA

##### HISTORICAL

The urethra may be the seat of the syphilitic process during all stages of the disease, although the chancre is by far the most frequent type of lesion found in this location.

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Fig. 2.—Large Hunterian chancre of peno-scrotal angle.



Fig. 3.—Large Hunterian chancre of penis.





Astruc<sup>4</sup> was probably the first to recognize chancre of the urethra. This astute writer described these lesions in both men and women and made the differential diagnosis between this condition and gonorrhea. A failure to recognize chancre of the urethra resulted disastrously to Hunter<sup>5</sup> when he performed his famous experiment of inoculating himself with the pus from a case of gonorrhea. From this experiment he drew false conclusions because undoubtedly there was also present a syphilitic lesion of this nature.

However, Ricord<sup>6</sup> taught that the urethra frequently lodged the syphilitic chancre and that it was due to this fact that many cases of syphilis remained unrecognized until further symptoms of the disease appeared.

The first recognition of other types of syphilis of the urethra was of a later date, in fact, for a long time their existence was denied by many authors. However, Virchow<sup>7</sup> in 1850 observed an ulceration of the urethra in a woman late in the course of the disease, while Nunn<sup>8</sup> in 1867 reported ten cases of stricture of the urethra due to syphilis of the so-called secondary period.

Since the work of these pioneers numerous observations of syphilis of both the male and the female urethra in all stages of the disease have been recorded.

#### CHANCRE

#### FREQUENCY

Chancre of the urethra is the least frequent of all genital chancres both in the male and the female. Fournier<sup>9</sup> found 17 chancres of the urethra in 414 genital chancres in men, and only 7 in 249 cases of genital chancre in women. Julien<sup>10</sup> observed 17 chancres of the urethra in 1773 genital chancres in men, while Tanton<sup>11</sup> found 5 in 83 cases. In 216 male genital chancres of which I have record, only 2 were situated in the urethra. I have, however, observed several cases of syphilis in the later stages in which from the history, or lack of history, and the failure to find genital scars I have concluded that the original infections were probably urethral.

*Location.*—The majority of urethral chancres in men are located only a few millimeters from the meatus and may be observed by spreading the meatal lips apart. Not infrequently, however, these

lesions are observed in the fossa navicularis, while occasionally they are found considerably deeper in the urethra.

*Pathogenesis.*—A number of theories have been advanced to account for the location of urethral chancres. It has been thought that after ejaculation the urethra aspirates fluid from the vagina, infection resulting. This theory, however, is rarely accepted today. In men with large meatal openings it is not improbable that infective material is simply forced into the urethra during copulation and chancres near the meatus result. Deep urethral chancres may result from the use of infected sounds or other instruments. And finally chancres of the urethra may occur as extensions from meatal lesions.

Urethral chancres in women probably usually result from the forcing of infective material (semen) into the canal during coitus, although, of course, in women urethral chancres may extend from meatal lesions as in men.

*Clinical History.*—Usually the first symptom of urethral chancre is a discharge, which begins from ten days to a month or more following coitus and is frequently considered both by the patient and the physician as gonorrheal. This discharge, however, is usually much less profuse than that of gonorrhea and is of a thin sero-sanguinous nature. It may rarely be thick, yellowish and profuse. There is rarely, even in the beginning, any pain on micturition.

On examination an indurated mass of varying extent may be palpated. This may be felt as a small nodule resembling a pea or small nut in the urethra, or it may be circular or ring like, more or less surrounding the canal, or finally it may extend for considerable distance along the urethra (even several centimeters) as a hard, indurated mass.

When the lesion is situated near the meatus it can usually be observed by spreading the lips of the meatus. In those cases in which it is located deeper in the urethra it may be observed by means of an endoscope.

In women with urethral chancre the discharge is usually so slight as to be overlooked. There may, however, be slight pain on micturition which calls the attention of the patient or the physician to the induration. This induration can best be determined by bimanual palpation, the index finger of one hand being introduced into

the vagina while the index finger of the other hand rests on the meatus.

The progress of urethral chancre in both men and women is sluggish as compared with most other syphilitic chancres, and this is accounted for by the passing of urine over it.

With this type of lesion there is a typical inguinal adenopathy and sometimes in men there is also a lymphangitis, dorsal to the penis which exists in the form of an indurated cord which is not painful.

*Diagnosis.*—Urethral chancre must be differentiated from *simple urethritis*, *gonorrhea* and the *later lesions of syphilis*. In simple urethritis there is usually little or no pain on urination, little inguinal adenopathy and neither gonococci nor spirochetes can be found on examination of the discharge, while no lump may be felt on palpation.

The discharge of gonorrhea is usually much more purulent than in chancre and gonococci can be found.

The later lesions of syphilis of the urethra are, as a rule, accompanied by other signs or symptoms of syphilis, and except in the macular type spirochetes cannot be found in the discharge.

Finally, the diagnosis of chancre of the urethra must rest upon the history, the serosanguinous discharge, the palpation of a lump in the urethra, the typical inguinal adenopathy and the finding of spirochetes in the discharge.

*Prognosis.*—As stated above the progress of urethral chancres is sluggish, although their retrogression takes place with comparative ease under the proper therapy. Upon healing there may be more or less stricture of the urethra.

*Prophylaxis.*—The prophylaxis of urethral chancre is the prophylaxis of syphilis and a discussion of this is not within the scope of the present paper.

*Treatment.*—The treatment of urethral chancre is the treatment of early syphilis, namely, intensive antisymphilitic therapy. Added to this it may be advisable to administer certain drugs, such as sandalwood oil, to render the urine less irritating.

#### OTHER LESIONS

As stated above, the occurrence of other lesions of syphilis than chancre in the urethra was denied for many years, but their occa-



sional existence is now beyond dispute. That they are not more frequently observed, particularly the macular type, would seem to be due, partially at least, to the fact that they rarely cause serious symptoms and are rarely looked for.

These lesions occur in three forms, a macular form, in all respects resembling the macular syphilomycoderm of other regions, as more or less isolated gummas, either single or multiple, and a rare form described by Fournier<sup>12</sup> as *cylindrical syphiloma*. There seems to be no reason why a papular type of lesion should not also occur, but as far as I am aware no such lesion has been reported.

#### MACULAR LESIONS

*Location.*—The macular lesions which have been observed have as a rule been found near the meatus, but some cases have been reported in which they were located deeper in the urethral canal. One case in particular is of interest. This case was reported by Tarnowsky<sup>13</sup> in 1872 and was in a male child of four who had been infected by its foster mother. At urination there was apparently severe pain, while the urethra was indurated and painful. On the twelfth day after entrance to the hospital the patient died and autopsy revealed the mucous membrane of the urethra and part of the bladder covered with superficial syphilitic ulcerations.

Sometimes the entire urethra seems to be inflamed and the term *syphilitic urethritis* might be applied with propriety.

*Clinical History.*—The first symptom to be observed in involvement of the urethra with macular lesions is usually an itching or tingling on urination. This is as a rule followed soon afterward by a slight viscid discharge. There may, however, be considerable pain on urination and the discharge may be mucopurulent, purulent, or even bloody.

*Diagnosis.*—The macular syphilomycodermata of the urethra must be differentiated from simple urethritis, gonorrhea, chancre of the urethra and gummatous lesions. As these macular lesions are almost always accompanied by other early manifestations of syphilis, remains of a chancre, syphilodermata, lesions of the mouth and throat, alopecia, etc., a diagnosis should not be at all difficult.

*Prognosis.*—The prognosis of the macular lesions of the urethra,

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Fig. 4.—Papular (miliary) syphilodermata of penis.



Fig. 5.—Chancre of the meatus. (Courtesy of Dr. M. B. Parounagian.)





like similar lesions elsewhere, is good as they readily heal under antisyphilitic therapy.

*Treatment.*—No other treatment than the use of the regular specifics is indicated in the macular syphilomycodermata of the urethra.

#### GUMMA

*Frequency.*—Gummas of the urethra are of comparative frequency. Fournier<sup>14</sup> found 19 such lesions in 151 cases of so-called tertiary syphilis of the penis. They may be primary, but much more frequently they occur as extensions from the adjacent tissues. In women primary gummas of the urethra are exceedingly rare, although as extensions they are more frequent than in men. They occur at nearly all stages of the disease being found as early as three months after the chancre, but usually at a much later date, ten, fifteen or even twenty years after infection.

*Location.*—Gummas of the urethra in the male are usually found in the posterior region of the penile portion of the urethra, although they have been found in all locations.

*Clinical History.*—Urethral gummas may be single or multiple and are observed as tumors of varying size from a pea to a marble, hard and round or hemispherical. They are painless at first, but if untreated these become soft and ulcerate and a more or less profuse purulent discharge develops. The ulceration may remain superficial, simply causing an erosion of the mucous membrane or it may be deep, destroying the adjacent tissues or even causing urethral fistulae.

There may or may not be painful and difficult urination, depending upon the size and location of the lesions and whether or not ulceration has occurred.

The healing of ulcerated gummas causes more or less stricture of the urethra due to cicatricial contraction.

*Diagnosis.*—Gummas of the urethra must be differentiated from tumors of other types, notably *epithelioma*, from *chancre* and from *gonorrhea*.

In *epithelioma* the induration is much less marked than in *gumma*, the patient is usually older, the seat of predilection in *epithelioma* is in the membranous portion of the urethra while gummas are more frequently found in the penile portion. Hematuria is frequent and

the pain of urination is more severe. A gumma develops more rapidly than epithelioma and there is no adenopathy in the former which occurs in the latter. Finally, the history and other evidence of syphilis including a positive Wassermann, may clear up the diagnosis; if not, one would be justified either in performing a biopsy for microscopical examination or trying the therapeutic test.

The differentiation from chancre rests upon practically the same points as the differentiation of chancre and gumma of the exterior of the penis, while the differentiation from gonorrhea is the same as the differentiation of chancre of the urethra and gonorrhea, except that in gumma spirochetes are rarely if ever found, although on the other hand the Wassermann is much more frequently positive. Also other evidences of syphilis are usually to be found.

*Prognosis.*—The prognosis of gumma of the urethra is not as good as that of chancre and the macular lesions, but under proper anti-luetic treatment healing should take place, although more or less stricture or other deformity, depending upon the extent of the lesions, will remain.

*Treatment.*—The usual treatment of late syphilis is indicated in gummas of the urethra, including arsphenamine, mercury and some form of iodide. Local measures are necessary in fistulae.

#### CYLINDRICAL SYPHILOMA

This rare syphilitic manifestation was first observed by Notta<sup>15</sup> in 1849 but not fully described until Fournier,<sup>16</sup> who observed six cases, did so. It occurs as a regular cylindrical infiltration of a segment of the urethra extending four to eight centimeters, rarely more, along the course of the canal. It has been described as feeling, upon palpation, like a pen holder or a pipe stem, but more aptly by Fournier as like a sound in the urethra. It may exist either with other manifestations of syphilis of the urethra, as isolated gummas, or it may exist entirely independently. Also there may be small nodules along the course of the cylinder which are gummas.

This type of lesion is made up largely of sclerous tissue and is therefore very resistant to treatment, more or less permanent contraction of the lumen of the urethra remaining.

## THE URETER

Lancereaux,<sup>17</sup> in 1866, wrote: "Syphilitic lesions of ureters and their pelves have not as yet been observed, and although there may be reason to believe that certain cases of hydronephrosis may have a syphilitic origin, it must be admitted that facts are yet wanting to establish this view with certainty."

In 1886 Hadden<sup>18</sup> exhibited a specimen before the London Pathological Society, in which the right ureter was obstructed by a mass which involved the bifurcation of the common iliac artery. The ureter was dilated to twice its normal size down to a point four and one-half inches from its entrance to the bladder. No microscopical examination of the mass is reported, but the statement is made that gummas were found in the liver and spleen.

## THE KIDNEY PELVIS

Syphilis of the pelvis of the kidney apparently is a most rare condition. Welz<sup>19</sup> in 1913, reported 2 cases, and Gottfreid,<sup>20</sup> in 1914, reported 1 case. In Gottfreid's case a cystitis and bilateral pyelitis which resisted bladder and pelvic lavage with silver nitrate, and in which the Wassermann was positive, cleared up under mercury treatment.

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## AGE OF THE RECIPIENT AS A FACTOR IN THE TOXICITY OF ARSPHENAMINE

BY GEORGE B. ROTH

*Pharmacologist, Hygienic Laboratory, U. S. Public Health Service,  
Washington, D. C.*

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AMONG the several factors responsible for variations in the toxicity of arspfenamine\* the age of the recipient was found to play a part in modifying the results of toxicity tests when observed under experimental conditions. The experiments herein reported were carried out primarily to ascertain whether it would be possible to use unselected rats, that is, rats in which the weight limits have not been defined, when conducting the official Hygienic Laboratory test upon arspfenamine intended for interstate and foreign commerce. This official test requires that white rats (*Mus-norvegicus albus*) ranging in weight from 100 to 150 grams shall be used. Since these weight limits are comparatively narrow, compliance with this requirement eliminates a large number of otherwise available animals and therefore adds to the difficulty of obtaining a sufficient supply through dealers.

According to Donaldson,† albino rats which have developed normally and which range in weight between 100 and 150 grams, are from 2 to 5 months old. Donaldson's figures from the Wistar Institute colony show that at 2 months of age, the males averaged 123 grams and the females 107 grams, while at 3 months of age the males averaged 185 grams and the females 148 grams. On the other hand, the figures which he gives for the New Haven colony of the Connecticut Agricultural Experiment Station show that at 2 months of age the males averaged 97 grams and the females 89 grams; at 3 months of age the males in the same colony averaged 144 grams

\*Arsphenamine is the American name for the dihydrochloride of 3,3' - diamino - 4,4' - dihydroxyarsenobenzene, and is frequently referred to as "606" or "Salvarsan."

†Donaldson, Henry H.: *The Rat*, Philadelphia, 1915.

and the females 115 grams, while females which averaged 150 grams were 150 days old (5 months).

From the above data it would appear that normal rats which range in weight from 100 to 150 grams are at least 2 months and not over 5 months old, and that a female of 150 grams is considerably older than a male of corresponding weight. Both males and females are sexually mature at 2 months of age and growth is quite rapid about this period. It is thus seen that the Hygienic Laboratory test requires that the rats used for the special tests on arspenamine shall be young, sexually mature, and in an active period of development.

In many of the experiments herein reported, practically the only criterion used with which to estimate the ages of the rats, was their weight. The weight will naturally vary depending upon such factors as diet, stock, care, etc., but if the animals are healthy they may be classified by means of weight into fairly definite groups as regards age. In those experiments in which the ages of the animals were definitely known, the growth curves deviate somewhat from those of Donaldson. The figures given by Donaldson which are quoted above represent averages and do not show the variations that may occur.

The first indication that age might be a factor in the toxicity of arspenamine for white rats was obtained from the following experiments. Two series of rats, series A and B, all of which were obtained from the same source of supply and which had received the same diet, were given intravenously and at the same rate 140 mgm. of arspenamine per kilo as a 2 per cent alkaline aqueous solution, each series having received a freshly made solution.\* Series A consisted of 10 rats all of which were slightly below regulation weight; series B of 10 rats all of which were much above regulation weight.

The results of these two series of experiments indicated that the rats below regulation weight were more resistant than those above regulation weight, 70 per cent of the small rats dying within 48 hours as compared with 100 per cent of the large ones. The experiments are given in detail in Table I.

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\*In all of the experiments herein reported, the injection rate varied only slightly, that is, the injection of each 1 c.c. of fluid required from two to two and one-half minutes; 0.9 c.c. of normal sodium hydroxide was invariably used to alkalinize each 0.1 gm. of arspenamine.

TABLE I

TOXICITY OF ARSPHENAMINE, LOT M, WHEN GIVEN INTRAVENOUSLY TO WHITE RATS AS A 2 PER CENT ALKALINE AQUEOUS SOLUTION PER LEG VEIN

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MOM.	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series A</i>						
6951	F	90	140	+	Died 12 hrs.	Mehring stock
6952	F	81	do.	+	Died 11 hrs.	do.
6953	M	88	do.	+	Died 2 hrs.	do.
6954	F	83	do.	+	do.	do.
6955	F	89	do.	+	Died 4 hrs.	do.
6956	F	73	do.	+	Died 20 hrs.	do.
6957	M	81	do.	-	Disch. 17 das.	do.
6958	M	88	do.	-	do.	do.
6959	M	92	do.	-	do.	do.
6960	M	98	do.	+	Died 6 hrs.	do.
<i>Series B</i>						
6851	M	275	do.	+	Died 6 hrs.	do.
6852	M	200	do.	+	Died 1 hr.	do.
6853	M	202	do.	+	Died 16 min.	do.
6854	M	215	do.	+	Died 1 hour	do.
6855	M	190	do.	+	Died 30 min.	do.
6856	M	218	do.	+	do.	do.
6857	M	216	do.	+	do.	do.
6858	M	188	do.	+	do.	do.
6859	M	212	do.	+	Died 1 da.	do.
6860	M	180	do.	+	do.	do.
Summary: Mortality within 48 hours						
Series A—70 per cent						
Series B—100 per cent						

The small animals used for the experiments in Table I rather closely approached the lower limits required by the regulations governing the testing of arsphenamine. In the next group (Group 2) of experiments, Series C, D, E, F, G, H and I, rats were selected which were either of regulation weight or much below regulation weight. These animals were all from the same stock and had received the same diet and care since birth. Each series, with the exception of Series D which consisted of 20 rats, comprised 10 rats, 5 being of regulation weight and the remaining 5 being much below the regulation weight. All rats of a given series received the same solution of arsphenamine intravenously and at the same rate in dosage of 160 mgm. per kilo. The injections were alternate with respect to the size of the rat so that any change which might occur in the toxicity of the solution as a result of standing would be equally borne by the two sizes of animals used in the experiment.



The results showed that out of 40 rats of regulation weight, only 11 rats or about 28 per cent survived for 48 hours, whereas out of the 40 rats much below regulation weight, 21 or about 53 per cent survived for a similar period. The details are given in Table II.

TABLE II

TOXICITY OF ARSPHENAMINE, LOT M, WHEN GIVEN INTRAVENOUSLY TO WHITE RATS AS A 2 PER CENT ALKALINE AQUEOUS SOLUTION PER LEG VEIN

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series C</i>						
13286	F	51	160	+	Died 3 hrs.	Hyg. Lab. stock
13287	M	112	do.	+	Died 2 das.	do.
13288	F	50	do.	+	Died 4 hrs.	do.
13289	M	127	do.	+	Died 12 hrs.	do.
13290	M	49	do.	+	Died 22 hrs.	do.
13291	M	120	do.	+	Died 14 min.	do.
13292	M	58	do.	-	Disch. 18 das.	do.
13293	M	110	do.	+	Died 12 hrs.	do.
13294	M	48	do.	-	Disch. 18 das.	do.
13295	F	112	do.	+	Died 2 das.	do.
<i>Series D</i>						
13301	M	115	do.	+	Died 6 hrs.	do.
13302	M	57	do.	+	Died 31 min.	do.
13304	M	63	do.	+	Died 4 hrs.	do.
13303	M	110	do.	+	Died 21 min.	do.
13305	M	125	do.	+	Died 19 hrs.	do.
13306	M	55	do.	-	Disch. 18 das.	do.
13307	M	104	do.	-	do.	do.
13308	M	57	do.	-	do.	do.
13309	M	106	do.	-	do.	do.
13310	M	62	do.	+	Died 15 hrs.	do.
13311	M	62	do.	-	Disch. 18 das.	do.
13312	M	112	do.	+	Died 35 min.	do.
13313	M	60	do.	-	Disch. 18 das.	do.
13314	M	110	do.	-	Died 5 das.	do.
13315	F	59	do.	-	Disch. 18 das.	do.
13316	M	119	do.	+	Died 12 hrs.	do.
13317	F	60	do.	+	Died 1 hr.	do.
13318	M	102	do.	-	Died 3 das.	do.
13319	M	64	do.	-	Disch. 18 das.	do.
13320	M	115	do.	-	do.	do.
<i>Series E</i>						
13421	M	108	do.	-	do.	do.
13422	M	70	do.	-	do.	do.
13423	M	113	do.	-	do.	do.
13424	F	54	do.	-	do.	do.
13425	M	111	do.	+	Died 14 hrs.	do.
13426	M	72	do.	-	Disch. 18 das.	do.
13427	M	124	do.	+	Died 19 hrs.	do.
13428	M	63	do.	-	Disch. 18 das.	do.
13429	M	98	do.	+	Died 2 das.	do.
13430	F	63	do.	-	Disch. 18 das.	do.

TABLE II—CONTINUED

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series F</i>						
13431	M	100	do.	-	do.	do.
13432	M	64	do.	-	do.	do.
13433	M	102	do.	+	Died 3 hrs.	do.
13434	M	52	do.	-	Disch. 18 das.	do.
13435	M	113	do.	-	Died 4 das.	do.
13436	M	56	do.	-	Disch. 17 das.	do.
13437	M	113	do.	+	Died 12 hrs.	do.
13438	F	58	do.	+	Died 3 hrs.	do.
13439	M	121	do.	+	do.	do.
13440	M	43	do.	-	Disch. 17 das.	do.
<i>Series G</i>						
13571	M	44	do.	+	Died 6 hrs.	do.
13572	M	101	do.	+	Died 1 hr.	do.
13573	M	43	do.	+	Died 6 hrs.	do.
13574	M	100	do.	-	Died 5 das.	do.
13575	M	48	do.	+	Died 18 min.	do.
13576	M	102	do.	+	Died 6 hrs.	do.
13577	M	56	do.	+	do.	do.
13578	M	115	do.	+	Died 7 hrs.	do.
13579	M	41	do.	+	Died 5 hrs.	do.
13580	M	113	do.	+	Died 7 hrs.	do.
<i>Series H</i>						
13581	M	45	do.	+	Died 1 hr.	do.
13582	M	106	do.	+	Died 9 hrs.	do.
13583	M	61	do.	-	Disch. 16 das.	do.
13584	M	110	do.	+	Died 9 hrs.	do.
13585	M	46	do.	-	Died 13 das.	do.
13586	M	113	do.	+	Died 6 hrs.	do.
13587	M	41	do.	-	Disch. 16 das.	do.
13588	M	105	do.	+	Died 9 hrs.	do.
13589	M	60	do.	-	Disch. 16 das.	do.
13590	F	105	do.	+	Died 5 hrs.	do.
<i>Series I</i>						
13591	F	101	do.	+	Died 2 hrs.	do.
13592	F	49	do.	+	Died 4 hrs.	do.
13593	F	103	do.	+	Died 1 hr.	do.
13594	F	45	do.	+	do.	do.
13595	F	121	do.	+	Died 4 hrs.	do.
13596	F	51	do.	+	Died 12 hrs.	do.
13597	F	104	do.	+	Died 1 da.	do.
13598	F	42	do.	+	Died 21 hrs.	do.
13599	F	130	do.	-	Died 4 das.	do.
13600	F	62	do.	+	Died 1 da.	do.

Summary, Series C, D, E, F, G, H and I.

Mortality within 48 hours:

Regulation weight—73 per cent

Below regulation weight—48 per cent.

A third group of experiments was then carried out on rats obtained from the same stock as those used in Group 2, in which the weight limits practically corresponded with those in Group 1, namely, rats of regulation weight and those much above regulation weight, the tests differing from those in Group 1 in that the injections were made alternately as regards the size of rats used.

In this group (3), 4 series, J, K, L and M, were employed, each series containing 5 rats of regulation weight and 5 much above regulation weight; all received the dosage of 140 mgm. per kilo.

The results again showed that the heavier rat was the less resistant to the drug. Necropsy showed that 3 of the rats of regulation weight which died were pregnant, while 3 of the rats much above regulation weight had pulmonary disease. Discarding these from our results we find that of the 17 normal regulation weight rats 5, or about 30 per cent, died, whereas of the 17 normal rats much above regulation weight 14, or about 85 per cent, died.

TABLE III  
TOXICITY OF ARSPHENAMINE, LOT M, WHEN GIVEN INTRAVENOUSLY TO WHITE  
RATS AS A 2 PER CENT ALKALINE AQUEOUS SOLUTION PER LEG VEIN

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series J</i>						
13686	M	122	140	+	Died 6 hrs.	Hyg. Lab. stock
13687	M	178	do.	+	Died 2 hrs.	do.
13688	M	122	do.	-	Disch. 16 das.	do.
13689	M	181	do.	+	Died 3 min.	do.
13690	M	141	do.	+	Died 2 das.	do.
13691	M	201	do.	+	Died 26 min.	do.
13692	M	108	do.	-	Disch. 16 das.	do.
13693	M	167	do.	-	do.	do.
13694	M	108	do.	-	do.	do.
13695	M	183	do.	-	Died 3 das.	do. caseous lungs.
<i>Series K</i>						
13696	M	202	do.	+	Died 12 min.	do.
13697	M	127	do.	+	Died 2 hrs.	do.
13698	M	153	do.	+	Died 11 min.	do. caseous lungs.
13699	M	121	do.	-	Disch. 16 das.	do.
13700	M	202	do.	+	Died 12 hrs.	do.
13701	M	102	do.	-	Disch. 16 das.	do.
13702	M	249	do.	+	Died 11 min.	do.
13703	M	107	do.	-	Disch. 16 das.	do.
13704	M	227	do.	-	do.	do.
13705	M	115	do.	-	do.	do.



TABLE III—CONTINUED

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series L</i>						
13716	M	130	do.	+	Died 1 hr.	do.
13717	M	206	do.	+	Died 25 min.	do. caseous lungs.
13718	M	124	do.	-	Disch. 15 das.	do.
13719	M	236	do.	+	Died 1 da.	do.
13720	M	111	do.	-	Disch. 15 das.	do.
13721	M	270	do.	+	Died 23 min.	do.
13722	M	135	do.	-	Disch. 15 das.	do.
13723	M	232	do.	+	Died 2 hrs.	do.
13724	F	108	do.	-	Disch. 15 das.	do.
13725	M	267	do.	+	Died 3 hrs.	do.
<i>Series M</i>						
13736	M	265	do.	+	Died 10 min.	do.
13737	F	122	do.	+	Died 43 min.	do. pregnant.
13738	M	261	do.	-	Disch. 15 das.	do.
13739	F	133	do.	+	Died 10 min.	do. pregnant.
13740	M	330	do.	+	Died 21 min.	do.
13741	F	111	do.	+	Died 5 hrs.	do. pregnant.
13742	M	322	do.	+	Died 9 hrs.	do.
13743	M	122	do.	+	Died 7 hrs.	do.
13744	M	362	do.	+	Died 29 min.	do.
13745	F	111	do.	-	Disch. 15 das.	do.

Summary, Series J, K, L and M.

Mortality within 48 hours:

Regulation weight—30 per cent.

Above regulation weight—85 per cent.

In the last group of experiments (Group 4), rats of known age were used, their weights approximating very closely those used in Group 2, namely, either of regulation weight or much below regulation weight. The animals ranged in age from 31 to 153 days and in weight from 30 to 175 grams. The treatment of all animals was identical, as to diet, care, dosage, etc.

This group comprised series N<sup>-1</sup>, N<sup>-2</sup>, O<sup>-1</sup>, O<sup>-2</sup>, P<sup>-1</sup>, P<sup>-2</sup> and Q<sup>-1</sup> and Q<sup>-2</sup> and consisted of 40 small and 40 large rats. The intravenous injections were alternate in respect to size and were all made at the same rate. Each series received a fresh solution of the drug. The results confirm the results obtained in the previous experiments very closely, that is that the younger animals are the more resistant to arsphenamine. This may readily be seen from the condensed report in Table V. The details, however, appear in Table IV.

TABLE IV

TOXICITY OF ARSPHENAMINE, LOT M, WHEN GIVEN INTRAVENOUSLY TO WHITE  
RATS AS A 2 PER CENT ALKALINE AQUEOUS SOLUTION PER LEG VEIN

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	AGE IN DAYS	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series N-1</i>							
20221	M	166	140	92	+	Died 30 min.	Hyg. Lab. stock
20222	M	91	do.	60	+	Died 3 hrs.	do.
20223	M	147	do.	92	+	Died 1 hr.	do.
20224	M	85	do.	60	+	Died 2 hrs.	do.
20225	M	155	do.	92	+	Died 3 hrs.	do.
20226	M	63	do.	60	-	Disch. 17 das.	do.
20227	M	118	do.	92	+	Died 1 hr.	do.
20228	M	66	do.	60	-	Disch. 17 das.	do.
20229	M	143	do.	92	+	Died 1 hr.	do.
20230	F	78	do.	60	+	Died 28 hrs.	do.
<i>Series N-2</i>							
20231	M	156	do.	95	+	Died 3 hrs.	do.
20232	M	97	do.	63	-	Disch. 17 das.	do.
20233	M	132	do.	95	+	Died 4 hrs.	do.
20234	M	103	do.	63	-	Disch. 17 das.	do.
20235	M	160	do.	95	+	Died 12 hrs.	do.
20236	M	85	do.	63	+	Died 3 hrs.	do.
20237	M	138	do.	95	+	Died 8 hrs.	do.
20238	F	97	do.	63	-	Disch. 17 das.	do.
20239	F	123	do.	95	+	Died 30 min.	do.
20240	F	95	do.	63	+	Died 1 hr.	do.
<i>Series O-1</i>							
20831	F	43	do.	31	-	Disch. 18 das.	do.
20832	M	132	do.	96	+	Died 1 da.	do.
20833	F	30	do.	31	+	Died 3 hrs.	do.
20834	M	127	do.	96	+	Died 1 da.	do.
20835	F	37	do.	31	+	Died 1 hr.	do.
20836	M	117	do.	96	+	Died 1 da.	do.
20837	F	48	do.	31	+	do.	do.
20838	M	128	do.	96	-	Disch. 18 das.	do.
20839	M	51	do.	31	+	Died 2 das.	do.
20840	M	106	do.	96	+	Died 1 da.	do.
<i>Series O-2</i>							
20841	M	58	do.	34	+	Died 1 da.	do.
20842	M	113	do.	98	+	Died 2 hrs.	do.
20843	M	61	do.	34	-	Disch. 18 das.	do.
20844	M	121	do.	98	+	Died 2 hrs.	do.
20845	F	48	do.	34	+	do.	do.
20846	M	117	do.	98	+	Died 1 da.	do.
20847	F	43	do.	34	-	Disch. 18 das.	do.
20848	M	100	do.	98	+	Died 1 da.	do.
20849	F	45	do.	34	+	do.	do.
20850	M	100	do.	98	+	do.	do.

TABLE IV—CONTINUED

NO. OF ANIMAL	SEX	WT. IN GRAMS	DOSE PER KILO MGM.	AGE IN DAYS	RESULT + = DIED - = LIVED 48 HRS.	TIME OF DEATH OR DISCHARGE	REMARKS
<i>Series P-1</i>							
21086	M	151	do.	101	+	Died 14 hrs.	do.
21087	M	62	do.	49	-	Disch. 14 das.	do.
21088	M	172	do.	101	+	Died 14 hrs.	do.
21089	M	71	do.	49	-	Disch. 14 das.	do.
21090	M	153	do.	101	+	Died 19 hrs.	do.
21091	M	53	do.	49	-	Disch. 14 das.	do.
21092	M	120	do.	101	+	Died 19 hrs.	do.
21093	F	55	do.	49	-	Died 11 das.	do.
21094	M	135	do.	101	+	Died 19 hrs.	do.
21095	F	53	do.	49	-	Disch. 14 das.	do.
<i>Series P-2</i>							
21096	M	130	do.	101	-	Disch. 14 das.	do.
21097	F	55	do.	49	-	do.	do.
21098	M	105	do.	101	-	do.	do.
21099	F	55	do.	49	+	Died 30 hrs.	do.
21100	M	92	do.	101	+	Died 19 hrs.	do.
21101	F	63	do.	49	-	Disch. 14 das.	do.
21102	M	137	do.	101	+	Died 19 hrs.	do.
21103	M	47	do.	49	+	Died 13 hrs.	do.
21104	M	137	do.	101	+	Died 19 hrs.	do.
21105	F	50	do.	49	+	Died 13 hrs.	do.
<i>Series Q-1</i>							
21766	M	68	do.	43	-	Disch. 14 das.	do.
21767	M	145	do.	130	+	Died 30 min.	do.
21768	M	63	do.	43	-	Died 6 das.	do.
21769	M	150	do.	130	-	Disch. 14 das.	do.
21770	F	68	do.	43	-	Disch. 14 das.	do.
21771	M	132	do.	130	+	Died 2 das.	do.
21772	M	95	do.	43	-	Disch. 14 das.	do.
21773	M	175	do.	130	-	Disch. 14 das.	do.
21774	M	80	do.	43	-	Disch. 14 das.	do.
21775	M	148	do.	130	+	Died 15 hrs.	do.
<i>Series Q-2</i>							
21776	M	66	do.	46	-	Disch. 14 das.	do.
21777	F	175	do.	153	+	Died 13 hrs.	do.
21778	M	74	do.	46	-	Died 7 das.	do.
21779	F	122	do.	153	-	Disch. 14 das.	do.
21780	F	68	do.	46	-	Disch. 14 das.	do.
21781	F	120	do.	135	+	Died 13 hrs.	do.
21782	F	62	do.	46	-	Disch. 14 das.	do.
21783	F	121	do.	135	+	Died 10 hrs.	do.
21784	F	59	do.	46	-	Disch. 14 das.	do.
21785	F	112	do.	135	+	Died 13 hrs.	do.

Summary—Series N-1, N-2, O-1, O-2, P-1, P-2, Q-1, Q-2.

Mortality within 48 hours:

Young—38 per cent.

Old—85 per cent.



TABLE V

TOXICITY OF ARSPHENAMINE, LOT M, WHEN GIVEN INTRAVENOUSLY TO WHITE RATS AS A 2 PER CENT ALKALINE AQUEOUS SOLUTION PER LEG VEIN

SERIES	LARGE		SMALL		NO. DIED WITHIN 48 HRS.		REMARKS
	NO. INJ.	AGE VARIATION IN DAYS	NO. INJ.	AGE VARIATION IN DAYS	LARGE	SMALL	
N <sup>-1</sup> and N <sup>-2</sup>	10	92-95	10	60-63	10	5	SMALL ONLY SLIGHTLY ILL IMMEDIATELY AFTER THE INJECTION
O <sup>-1</sup> and O <sup>-2</sup>	10	96-98	10	31-34	9	7	do.
P <sup>-1</sup> and P <sup>-2</sup>	10	101	10	49	8	3	do.
Q <sup>-1</sup> and Q <sup>-2</sup>	10	130-153	10	43-46	7	0	do.
Totals	40		40		34	15	
Per cent					85	38	

*General Summary and analysis of results:*

The above results unmistakably show that the weight limits of the animals should be rather strictly defined in the regulations governing the official testing of arspfenamine if reasonably concordant results are to be obtained. From this statement it must not be inferred that other factors, such as care, diet, etc., may be disregarded.

From a priori reasoning it would seem that the weight limits of the animals should be more narrowly defined than the present regulations require, that instead of using white rats weighing from 100 to 150 grams, those ranging from 100 to 120 or from 120 to 150 grams should be used. Nevertheless, if one compares the percentage of deaths obtained among rats weighing from 100 to 120 with those weighing from 120 to 150 grams, which can best be done by tabulations from Groups 3 and 4, one finds that the percentage of deaths among rats whose weights range from 100 to 120, is practically the same as among those whose weights range from 120 to 150 grams. It would seem, therefore, that the official weight limits are satisfactory. It is realized that the data upon which this conclusion is

based, are comparatively meager and may by a larger series be shown to be misleading.

Upon further analysis of these results it is observed that when more divergent weight limits are compared, the smaller, or younger rat is more resistant than the larger or older. Series A and B show that rats below regulation weight are more resistant than rats above regulation weight, whereas Series C, D, E, F, G, H and I show that rats considerably below regulation weight are more resistant than those of regulation weight. When we compare rats of regulation weight with those considerably above regulation weight as was done in Series J, K, L and M, we find that the regulation weight rats, in this case the smaller rats, are markedly more resistant than the larger rats. Group 4, which consists of Series N<sup>-1</sup>, N<sup>-2</sup>, O<sup>-1</sup>, O<sup>-2</sup>, P<sup>-1</sup>, P<sup>-2</sup>, Q<sup>-1</sup>, and Q<sup>-2</sup>, practically repeats the experiments in Group 2, except that in this case age can be definitely considered with weight. The results are similar to those of Group 3 and permit the conclusion that the smaller and younger rat is more resistant to arsphenamine than the larger and older rat. From this collective data we may conclude that the weights of animals which have developed normally, serve sufficiently to practically differentiate the young from the old animals, as was the method in the first three groups.

Since it has been shown that rats of regulation weight are less resistant than rats below regulation weight (all of which had been weaned) and more resistant than rats above regulation weight, one may conclude that there is apparently a gradual decrease in the resistance of white rats to arsphenamine as they increase in age from the weaning period. Their resistance previous to this period was not investigated nor was any attempt made to quantitatively determine the amount of decrease in resistance accompanying the increase in age from the weaning period.

*Clinical bearing of investigation:*

If we accept the assumption of Donaldson,\* 1915, that a rat three years old may be regarded as corresponding to a man 90 years old, our results herein reported if carried over to man, would apply largely to the period of development extending from the end of infancy to about the beginning of adult life. In Group 4, the rats

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\*Donaldson, Henry H.: *The Rat*, 1915.

ranged in age from 31 to 153 days (1 to 5 mos.) which would therefore correspond to the period in man extending from 30 months (2.5 years) to 150 months (12.5 years). These experiments therefore suggest that the clinician probably errs if in the administration of arsphenamine to children the dosage is proportionally smaller, per kilogram of body weight, in young than in older children as would be done if it is considered that the young child is less resistant than the older child. A dosage range of 0.05 gm. to 0.3 gm., when given intravenously, has been advocated for children. This would mean that if a boy of three who according to Holt and Howland,<sup>†</sup> should weigh about 15 kilos, were given the lower limit of 0.05 gm. he would receive less than .004 gm. per kilo, whereas if a boy of 12, who should weigh about 36 kilos, were given the upper limit of 0.3 gm., he would receive over 0.008 gm. per kilo or a proportional dose of about twice the size of that which the boy of 3 would receive.

The dosage of arsphenamine for syphilitic children advocated by various clinicians varies considerably. Of course many possible factors besides age must be considered in the clinical use of arsphenamine in these cases, such as the bodily nutrition of the individual, duration of the disease, involvement of the patient's various organs, especially the liver, kidneys and nervous system, weight, sex, unusual susceptibility to arsenic, etc. However, if we calculate the dosage for children in which all factors, except age and weight are alike, by basing our dosage on the above plan, we should undoubtedly be undertreating many children.

On the other hand certain clinicians advocate using 0.006 gm. of arsphenamine per kilo of body weight; that is, a boy of 3 weighing 14 kilos would receive 0.084 gm. and a boy of 12 weighing 36 kilos would receive 0.216 gm. This would seem to be the more rational dosage scheme in view of the above experimental results.

Many clinicians report that the reactions are fewer in the child than in the adult. This would suggest that the child is either receiving a dose too small or the adult a dose too large. Indeed in our cursory review of the literature we have failed to find a report of a death from the administration of arsphenamine to children, whereas many deaths were found to have occurred among adults.

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<sup>†</sup>Holt, L. Emmett, and Howland, John: *Diseases of Infancy and Childhood*, 1919, p. 19.



## CONCLUSION

These experiments permit the conclusion that the age of the recipient is a factor in modifying the results of toxicity tests on arsphenamine when observed under experimental conditions.\*

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\*Preliminary experiments with neoarsphenamine administered to 80 white rats, 40 weighing between 42 and 70 grams (series x) and 40 weighing between 101 and 135 grams (series y) indicate that age is also a factor in the toxicity of neoarsphenamine. In these experiments the small and large rats were injected alternately, and received the dosage of 240 mgm. per kilo, intravenously. The results were as follows: 33 out of the 40 in series x survived, whereas only 27 out of the 40 in series y survived the official observation period of seven days. Analysis of series N-1, N-2, O-2, P-1, and Q-1, in which the males predominate, shows that sex is not responsible for the above conclusion. In the above series, 14 out of 16 large male rats which were paired against 16 small male rats died, whereas only 4 of the 16 small died.

## SYPHILIS IN THE THIRD GENERATION\*

BY I. HARRISON TUMPEER, S.M., M.D., CHICAGO, ILL.  
*Associate Professor and Head of the Department of Pediatrics*

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**I**NHERITED syphilis practically presumes transmission to the second generation. What is the status of inheritance beyond this dead line? To fulfill the requirements of third generation transmission a chain of necessary conditions may be formulated after the manner of Koch's postulates for specific bacterial etiology of disease.

1. Acquired syphilis in a grandparent.
2. Certainty of the parentage of the affected parent.
3. Hereditary syphilis in that parent.
4. Absence of acquired syphilis in both parents.
5. Certainty of the parentage of the child.
6. Hereditary syphilis in the child.
7. Absence of acquired syphilis in the child.

In determining these points we must include the clinical signs and symptoms of acquired and hereditary syphilis, the serological reactions and demonstration of the spirochetes in the individual. The necessity for the first link in the chain of evidence is apparent. We must begin with acquired syphilis, and we must be sure of the parentage of the second generation member who is to transmit the disease. This consideration may be academic, but we require a pure second generation infection unaffected by the combination of an acquired and hereditary syphilis whose possibilities we shall see later. Third, one of the parents must show unmistakable evidence of hereditary syphilis. Such signs as transverse fissures across the lips and radiating scars at the corners of the mouth are absolutely pathognomonic and may obviate the necessity of actual data concerning the first two conditions. Fourth, the parents must be free from acquired syphilis because an individual with hereditary syph-

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\*From the Pediatric Clinic of the Post Graduate Medical School of Chicago.

ilis may also contract the acquired. The resulting offspring would be the product of what Tarnowsky<sup>1</sup> terms binary syphilis. Fifth, the parentage of the child of the third generation must be certain, again to exclude the possibility of an intervening genitor with acquired syphilis. Sixth, the child must have signs of hereditary syphilis, which at this stage tend to present themselves as dystrophies. Finally, the child must be free from acquired syphilis.

The difficulties in asserting third generation transmission are disagreements concerning the significance of dystrophic stigmata and absolute proof of parentage. Concerning the dystrophies one cannot escape the impression, even though statistical and sometimes serologic proof are wanting, that these are the results of syphilitic heredity. The fact that they may be also seen in alcoholic heredity and in unfavorable environment does not militate against their syphilitic origin, when such corroborative evidence is offered as a positive Wassermann test on blood and spinal fluid, notched teeth, primary optic atrophy, and delayed healing of bone in the young. Proof of parentage, strictly speaking, is impossible to obtain. The observer's knowledge of the parents and the resemblance of the child to the parents are all that can be presented. If the child has syphilitic stigmata like other cases of third generation syphilis, representing the contribution of the parent with the second generation infection, and at the same time resembles the normal parent, we have strong presumptive evidence of his exact origin.

These difficulties form the basis for the opinions that the requirements for third generation transmission cannot be fulfilled. It appears very plausible that there are many cases of third generation transmission whose requirements are fulfilled, but cannot be presented as established data. Is it impossible for an individual with hereditary syphilis to reach adult age, cohabit with an uninfected individual and bear offspring? The problem resolves itself in the demonstration of hereditary syphilis in the product of the union of a normal individual and one with inherited syphilis. The fact that not all the conditions can be demonstrated does not mean that this phenomenon cannot occur, although many adopt this attitude. In Fournier's<sup>2</sup> series of 45 cases he confesses the details are not complete, and he admits that one could refute the absolute value of the observations if there were not side by side cases with all the ele-



ments necessary as a basis of comparison. He further states that when one sees the resemblance of these observations with their neighbors one cannot escape the conviction that a common cause is at work. In other words, we must infer from cases whose evidence is complete that certain end results, as it were, which we see in children suspected of third generation syphilis and which resemble in all particulars the established cases, are also examples of third generation transmission. We cannot proceed to establish the links in a chain of evidence extending over half a century as we would establish Koch's postulates, whose materials and conditions we may manipulate at will.

To Hutchinson we attribute most of our knowledge concerning inherited syphilis. His statements on the question of third generation transmission are uncertain and in some respects wrong. He lacked serologic and parasitologic data, we now possess, which would have altered some of his views. In 1899,<sup>3</sup> he stated that "it is improbable in the highest degree that those who have long ceased themselves to be liable to manifestations of syphilis should still be capable of transmitting it." He did not have the Wassermann reaction; he was thinking of active lesions. He further stated that "in order that either contagion or transmission should be possible we must suppose that the specific virus is still extant, and all the facts with which we are acquainted converge to the belief that the duration of its life in the system is in almost all cases limited." Recent work, which we will consider further, would have illuminated the question of duration of the specific virus in the host. In 1900,<sup>4</sup> he relented somewhat by saying that it was improbable that a taint, which ceased to be effective as a contagion, could still continue to cause inherited transmission. He did not believe that the tertiary symptoms, those present after the infection had perished, as he expressed it, could be transmitted. He believed<sup>5</sup> that two years after a man contracted the disease he would no longer transmit the infection and that this had an important bearing on the question because it takes at least twenty years before the child of syphilitic parents becomes himself a parent. We know the two year period is inaccurate. Hutchinson further argued that the first born who show symptoms after two years of parental infection show acquired and not hereditary syphilis since the symptoms of the inherited are dis-

tinct from the acquired. He said that if the disease is transmitted the child must have a rash and infantile symptoms and that these symptoms, however slight, must occur within the first few months of life. He also introduces a family of which he says that if it were one of third generation transmission we must accept that the wife is liable to bear tainted children at a seven year interval without infecting her husband who lived with her all the time. In our case the father of the children has lived with the mother for eleven years without being infected.

Keyes<sup>6</sup> does not believe in third generation transmission on the grounds that a man's capacity to transmit syphilis to his wife almost ceases within five years and a woman's capacity to bear syphilitic children within ten years. It seems to the last degree improbable, he says with Hutchinson, that a child born syphilitic should retain the power of transmitting the disease until he reaches maturity.

To comprehend the objections of other writers it is necessary to introduce the term binary syphilis. This name is applied by Tarnowsky to designate the condition of acquired syphilis superimposed upon an individual with hereditary syphilis. This is not impossible as it may at first appear. There are authenticated cases on record of the development of chancre in individuals with inherited syphilis. Jullien<sup>7</sup> refers to an undoubted hereditary syphilitic who acquired a chancre at 20 years with all the usual consequences. He collected 93 such cases. The chief objectors to the third generation idea argue that an individual with binary syphilis transmits the acquired and not the hereditary disease.

Among the advocates of third generation transmission Finger<sup>8</sup> states it may be transmitted sometimes as dystrophies due to syphilotoxin, rarely as true virulent syphilis, and, thirdly, as immunity. He thinks the dystrophies are hard to consider because they do not resemble the characteristics of syphilis. From the collected evidence it seems that the dystrophies are the peculiar characteristics of the late transmission of syphilis. Along these lines Fournier<sup>9</sup> strongly believes in the third generation phenomena. He says it kills two-fifths of its members and usually shows itself in four-fifths of the cases by dystrophic stigmata similar in every way to inherited

syphilis. In 14 per cent of cases under his observation it exhibited symptoms of virulent syphilis.

In a consideration of third generation transmission it is curious to note that Gaucher<sup>10</sup> reported a case of transmission to the fourth generation. He had treated the grandfather of the children who were in the fourth generation. The great grandfather died of a syphilitic paraplegia early in life.

Tarnowsky concludes that acquired syphilis shows its chief influence on the second generation. It affects the third generation feebly. Its influence diminishes to the fourth generation and seems to cease there.

As long as the Wassermann test was unknown and the spirochete had not been demonstrated, observers were handicapped in checking their cases and had to depend entirely on clinical signs. However, most of the objections that are offered partake more of the nature of opinion than proof. If we can demonstrate the spirochete in the individual we may render plausible the transmission of syphilis from those with old infections. This has been done and largely upsets Hutchinson's and Keyes's ideas of the limits of syphilitic transmission and the duration of active infection. Resistant forms of the spirochete have been called upon as an explanation for latency of syphilitic infection. However, Noguchi<sup>11</sup> could not find any evidence to support such an idea although he says that the spirochete under favorable conditions is one of the most viable of organisms. In suitable media it survives a year at 37° C., and under naturally favorable conditions it may remain dormant for years. In support of this opinion is the work of Graves<sup>12</sup> who succeeded in infecting rabbits by injecting the blood of a patient whose initial infection dated back thirty years. The sample of blood had been kept 310 days. Another specimen kept for fifteen months before injecting was obtained from an individual whose initial infection occurred 23 years before, and this also gave a positive result. Furthermore, Eberson and Engelman<sup>13</sup> produced typical syphilitic lesions in rabbits' testicles and recovered and propagated the organism for an indefinite number of generations. They used semen and inguinal gland material isolated from patients giving histories of syphilis of 11 and 13 years standing in two instances and 1 year in three instances. One of these cases proved positive in



material from the inguinal gland of a man whose Wassermann reaction had been negative following treatment and at the time of taking the specimens was two plus only in the cholesterinized antigen. A second instance of this kind was found in the case of a specimen of semen which proved positive for the spirochete. The other significant point was the evidence that the spirochetes had not lost their virulence for rabbits. Zinsser and Hopkins<sup>14</sup> found there was no consistent change either in decrease or increase of pathogenicity during progressive rabbit passage. There was no difference in the pathogenicity of the organism from different sources. The same results were obtained from spirochetes found in condylomata, chancres, mucous patches, and from one of the central nervous system. This last finding gives experimental confirmation of clinical experience, namely, that an individual with nervous syphilis may transmit syphilis to his offspring. Further work will probably demonstrate the spirochete in the tissues of the third generation.

#### REPORT OF CASES

From the clinical standpoint the following data is offered, strongly presumptive of third generation transmission. A child of six years was brought to the clinic by her parents. Following our custom, we studied the child's appearance an instant before taking the routine history and performing the examination. One was struck by the vague appearance of a defective child. A glance at the mother made the story plain. She had a hunted, stary, defective look, protruding, tusk-like, pyorrheal incisor teeth, and the picture culminated in significant fissures across the lips and radiating scars at the corners of the mouth. The father looked healthy and normal. A visit to the home revealed a squalor beyond belief. In addition a veritable mine of spirochetal treasure was unearthed. A girl of fourteen with strabismus and Hutchinson teeth spread a sickly grin as she ran out to school. One boy of nine years was blind. This boy and a brother of five years had large broad heads with the thickening more marked in the parietal regions. Suspicious of social agencies the parents prevented further examination and investigation. Seven months later fortuitous circumstance impelled a second visit to this home. That day the girl of the ghastly grin had been thrown to a cement pavement by playmates and was lying

in coma in a neighbor's house. From this time diplomatic practice paved the way for further contact and study.

The mother (Fig. 1) of the children is thirty-eight years old. Her mother died of asthma about the age of fifty years. Her father died of dropsy about the same age, but no further record could be found at the hospital. There is one sister forty-two years old who appears normal and is married to a normal appearing German printer. There are two children in this family. The elder, twenty years old, is a student of engineering, and the younger, sixteen years old, attends high school. These attainments are in marked contrast with the children with whom we are more directly concerned. The social status of the two families is widely different, and the sisters are practically strangers to each other. The defective one resents all assistance and interference from the elder, who avoids the situation for fear of abuse. The family of the elder sister is self-respecting and progressive. We were unable to make detailed study of its members or obtain Wassermann tests. Undue enthusiasm could not be manifested because of the possibility of creating domestic doubt and difficulty.

The family with which we are concerned are the dregs of society. The father is Italian, and the mother Irish American, both of the poorer types. They live in a neighborhood of Italians of the laboring class mixed with the lowest of other nationalities. They have four mean rooms, and all the children sleep in one bed. Clothing, food, and home conditions haunt one with their ugliness. The first husband of the mother is living as far as is known. He was a soldier before his marriage and had been apparently well. He was Irish and evidently came from a self-respecting family. He deserted the sinking or sunken ship in 1908, leaving the girl of the ghastly grin as his contribution. Whether or not the usual form of marriage was observed in her second venture is not stated. However, the second genitor is well developed and normal physically. A Wassermann test on his blood was found negative by two different laboratories. The mother has been pregnant six times. There were no miscarriages or stillbirths. The child of the third pregnancy died at three months from a summer disease.

The eldest girl (Fig. 2) is the child of the first husband. She is now fifteen years old. At nine years of age she was treated at

the Post Graduate and Cook County Hospitals for interstitial keratitis. The Wassermann test at this time was four-plus. The history stated that there was no snuffles or rash in infancy. At the time of her hospital admission there were noted nasal discharge and marked notching and peg shape of the upper incisors. The tonsils were removed subsequently, and again the blood was reported four-plus. In February, 1921, she was thrown to the cement floor of the school basement, striking her head. She became comatose, but the next day she could be aroused and complained of difficulty of vision. After a few days of unknown medication by another physician she was brought to the Post Graduate Hospital where vigorous antisyphilitic treatment was begun. To describe her condition briefly: the upper incisors were the typical peg shaped, notched variety situated higher in the jaw than their fellows. There was no vomiting. The blood pressure was normal, and the urine was free from sugar. There was occasional paresis of the right side of the face. The tongue deviated slightly to the left. There were no pathological reflexes, and the stereognostic sense was good as a rule. The gait was sometimes unsteady, and at times the Romberg sign was indicated. She complained of abdominal pain at times, and there was somewhat diminished pain sense over the tibiae. There were several seizures resembling epilepsy. The Wassermann test on the blood and spinal fluid was a doubtful negative. There had been a short period of treatment six years before.

After her discharge from the hospital there were several epileptiform seizures. Some were apparently staged. She was unwilling to return to her home, and whenever her mother was announced she would turn away, pout or pretend a fit. During the seizures and to some extent between attacks there is a remarkable catatonia. She proved an unreliable escort to her younger brother, who attends a special blind class to which we have sent him, and has a tendency toward truancy. How much of her behavior is due to the meddling of the woman who took her into her home directly after the injury is not clear. This woman apparently antagonized the child against her mother and was eager to adopt this girl of the ghastly grin had the courts been willing, although her four puny offspring might properly be candidates for any additional interest this would-be foster mother might bestow. In March, 1921, Dr. David Levy of the





Fig. 1.—Mother of the children. Note the fissures of lips and the general expression.



Fig. 2.—Eldest child, daughter of the first husband. Note the notched teeth set high in the jaw and strabismus.



Fig. 3.—Eldest of the children of the second husband. Note the excavation of the tips of the upper incisors. The inequality of the pupils may be seen. This boy has primary optic atrophy and a large dystrophic head.



Institute of Juvenile Research examined the girl. He found her to score about nine and one-half years, placing her in the high grade defective group. He stated it was difficult to differentiate the inherent defect due to syphilis and that due to inherited mentality as such. Her attitude was characterized by lapses of attention which would probably show different results in further scores. Some of her reactions were considered definitely pathologic. There was better ability in immediate memory than in other tests, and she was especially poor in tests involving comprehension.

The next child (Fig. 3) is now nearly ten years old. He was apparently well until January, 1920, when he was struck by an army truck, fracturing his femur. He was comatose following the accident. It is significant that healing was delayed and that four months later he developed primary optic atrophy. The fracture was finally corrected by a bone graft, and treatment for syphilis was carried out at the same time. The Wassermann test on the blood in June, 1920, was four-plus. The quadrilateral shape of the head was noted at this time. In February, 1921, we were enabled to admit him to the Post Graduate Hospital for study following our negotiations concerning the sister. The head is very broad particularly in the parietal regions. He is completely blind. There are no headaches, vomiting or bradycardia. The upper incisors are not peg shaped or situated high in the jaw, but at their lower margins there can be seen arch shaped excavations as if typical notching would have resulted had the process gone further. The spleen is not palpable. There are no abnormal reflexes except the pupillary. There are excoriations of the upper lip from the nasal discharges. The x-ray showed thickening of the frontal bone particularly of the outer table at the frontal eminences. The entire skull shows thickening of the external table. The sella is flattened and elongated in the anteroposterior direction. The cranial area is disproportionate to the face being very much larger than normal. These findings were also noted in an x-ray taken at the Cook County Hospital. His weight was 62 pounds, 6 pounds more than the average for his age and height, height 48 inches, sitting height 25.5 inches, biparietal diameter 16 cms., bifrontal 13 cms., occipito-frontal 19 cms., suboccipito-frontal 17.5 cms., mento-occipital 23 cms., suboccipito-frontal circumference 46 cms., occipito-frontal cir-



cumference 49 cms. The middle of the external auditory meatus is 10 cms. from the frontal plane and 7.8 cms. from the posterior. A mental test by Dr. Levy scores him seven and one half years, placing him in the subnormal but not feeble-minded group. Again there is difficulty in differentiating the inherent defect due to syphilis and that due to inherited mentality as such. This child, too, was characterized by lapses of attention which would probably show different results in further scores. There was better ability in immediate memory than in other tests. He was especially poor in tests involving comprehension. The Wassermann test on the blood and spinal fluid was four-plus.

There are three other children. The girl of 7 years, who was first brought to the clinic, has a constant nasal discharge. Her mouth hangs open. She is shy and looks stupid. Her head is normally shaped, and her stature approximates the normal. The Wassermann test on her blood is negative.

A boy of six years has a large head like his brother. He is very timid and also looks stupid. His height is 39 inches; his sitting height 22 inches. He is about three inches underheight for his age. The bifrontal diameter is 11.5 cms., biparietal 14.5 cms., occipito-frontal 19 cms., suboccipito-frontal 17.5 cms., mento-occipital 21.5 cms., suboccipito-frontal circumference 45 cms., occipito-frontal circumference 47 cms. His Wassermann test is negative.

A girl of three years is chubby, timid and stupid looking. She, too, has a constant nasal discharge, and her Wassermann test is negative.

#### DISCUSSION

The history, physical signs, and serologic tests demonstrate that the present genitor is free from syphilis, acquired or hereditary. The mother has hereditary syphilis which is betrayed by the fissures across the lips and radiating sears at the corners of the mouth. She states that she has had these marks all her life but no notice had been taken previously. This finding is only present in hereditary syphilis and can only be imitated by making fine incisions early in life, which constitutes *reductio ad absurdum*. Hochsinger<sup>15</sup> makes the very definite statement in corroboration of this view that an absolutely positive proof of former hereditary syphilis is found in the radial scar formation on the lips. That syphilis is present is

demonstrated in the four-plus Wassermann reaction on the mother's blood.

Concerning the first husband we have no data. However, had the mother acquired syphilis in addition to her inherited disease we should expect miscarriages, stillborn children, or children with syphilitic manifestations at birth or within the first few months. This does not conform with the facts in our case. The first child was carried to term, had no infantile symptoms and revealed her first signs in the teeth of the second dentition and an eye affection at nine years. It might be argued that the mother's inherited disease altered the usual course by the presence of a relative immunity. This is contradicted by the fact of the theoretically acquired infection which could not have occurred if immunity were present. It is Tarnowsky's contention that a child of a parent with binary syphilis inherits the acquired and not the hereditary form. Yet the first child gave evidence of her heredity late and passed through uterine life and infancy apparently clear. It is difficult to conceive how the child would be uninfluenced by the maternal inherited syphilis.

The second genitor has escaped infection from his wife with a four-plus reaction although he has lived with her for eleven years. This brings additional proof to Hutchinson's statement that apparently a wife may bear syphilitic children for a seven year interval without infecting her husband who has lived with her all the time. He came to this conclusion in a family which evidently was one of third generation transmission.

The four younger children are the offspring of this healthy father and the mother with, at least, hereditary syphilis. The children all resemble the father in form and feature. There is no reasonable doubt that he is the father. It may satisfy some doubts to state that although she apparently waived the legal formality of marriage, the mother adheres tenaciously to a definite code of morals as is indicated in her scorn of those neighbors not above suspicion. The only factor we have to consider is the mother. Facts have been introduced to suggest that there is no probability of superimposed acquired infection. Absolute proof is impossible to present any more than absolute proof of parentage is possible to present. However, all facts speak against the presence of acquired syphilis unless we relegate to directly inherited syphilis unusual phenomena, phe-

nomena which have been described by others in large numbers of observations as peculiar to the manifestations of syphilis which has been transmitted further than the second generation. Examples of this are the dystrophic stigmata. In our particular case, there have never been miscarriages, stillbirths, or infantile signs of syphilis. Only one child of six pregnancies died. This child died at three months, and was said to have a summer infection, which we cannot consider surprising in such surroundings. Of the children that lived active signs of syphilis were not manifest until late in childhood. The stigmata are evident early. The dystrophic heads are present early. Although the eldest had Hutchinson teeth and a nasal discharge, interstitial keratitis was not apparent until nine years. Her nervous and mental abnormalities developed following trauma. That is to be remarked. The next child, son of the second genitor, had the large head, but there were no active signs of syphilis until the trauma occurred with subsequent primary optic atrophy and the bone, itself, was slow in healing. The three younger children have negative blood tests and show no active signs of syphilis at present although all have constant nasal discharges and the boy has the typical dystrophic stigmata of head and stature. Will trauma excite active lesions on the predisposing soil of heredity?

It is very evident that these are not the usual cases of inherited syphilis. Comparison with other cases of third generation transmission corroborates this view as we noted earlier. It is to this class of case that Fournier referred when he said we cannot escape the impression that a common cause is working when we compare these findings with those of cases of third generation transmission in which all the links in the chain of evidence are complete. These children have not acquired syphilis, resulting as in one case optic atrophy, because the stigmata were present before the development of the active lesions. In the case of the three younger children the future appearance of juvenile paresis or tabes, or primary optic atrophy cannot be ascribed to acquired infection. The stigmata of inherited syphilis are present now despite the Wassermann reaction which is variable. The girl with the Hutchinson teeth who twice had four-plus reactions now shows a negative test despite only meager treatment. The spinal fluid of the younger children was not



obtainable, and who knows but what a trauma will change the serological reactions?

#### CONCLUSIONS

1. Four children from a healthy father and a mother with inherited syphilis have been affected by secondary inheritance.
2. The father, who has lived with the mother for eleven years, has escaped infection.
3. The first child by a previous father has also inherited syphilis from the mother with inherited syphilis.
4. Trauma is important in the development of active lesions in hereditary syphilis.

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## STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION. XXI\*

### A STUDY OF METHODS FOR CONDUCTING THE SECONDARY INCUBATION AND TIME OF READING OF COMPLEMENT FIXATION REACTIONS IN SYPHILIS

BY JOHN A. KOLMER, M.D., PHILADELPHIA, PA.

*From the Dermatological Research Institute of Philadelphia*

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THE method of conducting the secondary incubation in the Wassermann test for the purpose of detecting the degree or amount of complement fixation, has not attracted much attention. Many workers follow Wassermann's custom of conducting this phase of the test in an air incubator at 37° C. for an arbitrary period of one hour; others use longer periods up to two hours. Probably the majority of serologists employ a water-bath at 37° to 38° C. for arbitrary periods varying from fifteen minutes to an hour or more; others use the air incubator or water-bath and remove each set of tubes as the controls show complete hemolysis, instead of allowing them to remain for a fixed and arbitrary period.

Contrary to general opinion the matter of choosing a method is not one of convenience only and especially in tests conducted with an antishoop hemolytic system; the presence of natural hemolysins in the sera exert an important influence upon the results of quantitative tests, especially with weakly positive sera, and influence the choice of a method for conducting the secondary incubation.

Furthermore the time of reading the reactions is a matter of practical importance and especially with an antishoop system. Wassermann originally advised placing the tubes in a refrigerator after the second incubation to permit the settling of corpuscles before the readings were made; probably the majority of workers at the present time follow this custom while others read immediately after the secondary incubation, or after the tubes have stood at room temperature for an hour or two.

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

## PURPOSES OF INVESTIGATION

The purposes of this investigation were to submit these methods to comparative tests after the following plan, in order to choose the best practices for a standardized complement-fixation technic:

1. To make comparative studies of different methods for conducting the secondary incubation for the degree of complement fixation.
2. To determine the best time for reading the reactions.

## Part 1

## METHODS OF SECONDARY INCUBATION

*Incubator versus Water-bath.*—Syphilitic and nonsyphilitic sera were tested with an antisheep system (1) by setting up two sets at the same time and under identical conditions with a primary incubation of eighteen hours at 8° C.; next day, hemolysin and corpuscles were added to the cold tubes of each set and secondary incubation conducted in an air incubator at 37° C. and in a water-bath at 37° C. for one hour. All tests were rendered quantitative by using each serum in graded amounts; the readings were made an hour after the completion of the secondary incubation. The results observed with ten sera are shown in Table I as examples of the series; these results may be summarized as follows:

TABLE I  
INCUBATOR VERSUS WATER-BATH FOR THE SECONDARY INCUBATION; ANTISHEEP  
HEMOLYTIC SYSTEM

NO.	INCUBATOR SET *						WATER-BATH SET **					
	TIME FOR HEMOLYSIS	0.1	0.02	0.004	0.0008	CONTROL	TIME FOR HEMOLYSIS	0.1	0.02	0.004	0.0008	CONTROL
1	60 min.	4	4	—	—	—	45 min.	4	4	—	—	—
2	60 "	4	4	4	1	—	60 "	4	4	2	—	—
3	35 "	4	4	—	—	—	25 "	4	4	—	—	—
4	60 "	4	4	—	—	—	40 "	4	4	—	—	—
5	60 "	4	4	4	—	—	60 "	4	4	4	—	—
6	60 "	4	3	1	—	—	40 "	4	3	—	—	—
7	60 "	4	3	—	—	—	20 "	4	3	—	—	—
8	35 "	4	3	—	—	—	20 "	4	3	—	—	—
9	60 "	4	4	3	—	—	60 "	4	4	3	—	—
10	35 "	4	4	1	—	—	25 "	4	4	—	—	—

\*Hemolytic control required 38 minutes; antigen control required 45 minutes.

\*\*Hemolytic control required 15 minutes; antigen control required 25 minutes.



1. Hemolysis in the water-bath is more rapid than in an air incubator; with the majority of sera the controls in the water-bath showed complete hemolysis in about one quarter to one half the time required in the air incubator. For this reason the water-bath is more convenient.

2. *Secondary incubation in the air incubator, however, occasionally yielded more delicate reactions than observed in the water-bath;* this is explained by the fact that the tubes warm up more slowly and permit the greater fixation of complement by syphilis antibody and tissue extract before a temperature is reached at which hemolysis is favored.

*Temperature in Relation to Secondary Incubation.*—To bring this fact out more clearly additional experiments were conducted with an antisheep system<sup>1</sup> by setting up five sets with each of a series of syphilitic and nonsyphilitic sera, and after a primary incubation of eighteen hours at 8° C. adding hemolysin and corpuscles to the cold tubes and conducting the secondary incubations in water-baths at 25°, 30°, 35°, 38° and 40° C. The results observed with ten of these sera are shown in Table II as examples.

1. The optimum temperature insofar as concerns rapidity of hemolysis in a water-bath is from 35° to 40° C.; hemolysis at 40° C. is somewhat more rapid than at 35° C.

2. With lower temperatures varying from 25° to 35° C. hemolysis is slower, but the reactions are more delicate due, probably, in part, to the fixation of more complement by syphilis antibody and tissue extracts at these lower temperatures before hemolysis takes place.

3. Secondary incubation at 25° C. is, however, too slow for practical purposes and with some sera results in incomplete hemolysis of the controls.

4. The optimum temperature for secondary incubation in a water-bath from the standpoints of sensitiveness and practicability is from 35° to 38° C. with an average of 37° C.

*The Influence of Preliminary Warming of Tubes in a Water-bath before the Addition of Hemolysin and Corpuscles.*—As stated in a previous article<sup>2</sup> if the tubes are placed in a water-bath at 37° C. for one hour after a primary incubation of eighteen hours at 8° C. before the addition of hemolysin and corpuscles, the reactions are rendered somewhat more sensitive. This result is due not only to a

TABLE II  
THE INFLUENCE OF TEMPERATURE UPON THE SECONDARY INCUBATION

NO.	WATER-BATH AT 25° C.				WATER-BATH AT 30° C.				WATER-BATH AT 35° C.				WATER-BATH AT 38° C.				WATER-BATH AT 40° C.			
	0.1	0.02	0.004	0.0008	CONTROLS <sup>a</sup> HEMOLYSIS	0.1	0.02	0.004	0.0008	CONTROLS <sup>a</sup> HEMOLYSIS	0.1	0.02	0.004	0.0008	CONTROLS <sup>a</sup> HEMOLYSIS	0.1	0.02	0.004	0.0008	CONTROLS <sup>a</sup> HEMOLYSIS
1	—	—	—	—	35 min.	—	—	—	—	15 min.	—	—	—	—	15 min.	—	—	—	—	90 min.
2	—	—	—	—	2 hrs.	—	—	—	—	30 min.	—	—	—	—	30 min.	—	—	—	—	Not in two hours.
3	4	4	3	—	2 hrs.	4	4	3	—	1 hr.	4	4	3	—	1 hr.	4	4	3	—	Not in two hours.
4	4	4	3	—	2 hrs.	3	3	3	—	2 hrs.	3	3	3	—	2 hrs.	3	3	3	—	Not in two hours.
5	4	4	4	—	1½ hrs.	4	4	4	—	30 min.	4	4	4	—	30 min.	4	4	4	—	Not in two hours.
6	4	4	4	—	1½ hrs.	4	4	4	—	40 min.	4	4	4	—	30 min.	4	4	4	—	Not in two hours.
7	4	4	4	1	1½ hrs.	4	4	4	2	40 min.	4	4	4	3	1 hr.	4	4	4	3	Not in two hours.
8	4	4	4	1	1½ hrs.	4	4	4	1	40 min.	4	4	4	3	30 min.	4	4	4	4	Not in two hours.
9	4	4	2	—	35 min.	4	4	4	—	25 min.	4	4	2	—	30 min.	4	4	3	—	Not in two hours.
10	4	3	—	—	40 min.	4	3	—	—	30 min.	4	3	—	—	25 min.	4	4	3	—	1½ hrs.

TABLE III  
THE INFLUENCE OF PLACING TUBES IN A WATER-BATH AT 38° C. FOR FIVE TO THIRTY MINUTES BEFORE THE ADDITION OF  
HEMOLYSIN AND CORPUSCLES. PRIMARY INCUBATION 18 HOURS AT 8° C.; ANTISHEEP SYSTEM

NO.	HEMOLYSIS AND CORPUSCLES ADDED TO COLD TUBES				ADDED AFTER 5 MINUTES IN WATER-BATH				ADDED AFTER 15 MINUTES IN WATER-BATH				ADDED AFTER 30 MINUTES IN WATER-BATH			
	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL	CONTROL
	4°	4	1	—	—	4	4	3	—	—	4	4	3	—	—	—
1	4	4	1	—	—	4	4	3	—	—	4	4	3	—	—	—
2	4	4	1	—	—	4	4	1	—	—	4	4	1	—	—	—
3	4	4	1	—	—	4	4	1	—	—	4	4	1	—	—	—
4	4	4	4	4	—	4	4	4	4	—	4	4	4	4	—	—
5	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	—
6	4	4	4	4	—	4	4	4	4	—	4	4	4	4	—	—
7	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	—
8	4	4	4	1	—	4	4	4	1	—	4	4	4	1	—	—
9	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—	—
10	4	4	4	2	—	4	4	4	3	—	4	4	4	3	—	—
11	4	3	—	—	—	4	4	—	—	—	4	4	—	—	—	—
12	1	1	—	—	—	1	1	—	—	—	2	2	1	—	—	—
13	4	4	4	3	—	4	4	4	3	—	4	4	4	3	—	2
14	4	4	4	3	—	4	4	4	3	1	4	4	4	4	—	—
15	4	4	2	—	—	4	4	2	—	—	4	4	3	—	—	—
16	4	4	4	3	—	4	4	4	3	—	4	4	4	3	—	—
17	4	4	1	—	—	4	4	2	—	—	4	4	2	—	—	—
18	4	4	3	—	—	4	4	4	—	—	4	4	4	—	—	—

\*4 equals ++++; 3 equals +++; 2 equals ++; 1 equals +.



greater fixation of complement by syphilis antibody and tissue extract, but also to greater nonspecific fixation of complement by extract alone and sera alone and to a greater destruction of complement; these nonspecific factors outweigh the slight advantage of enhanced specific fixation and, therefore, the combined primary incubation of eighteen hours at 8° C. plus one hour at 38° C. could not be recommended.

However, with the technic employed in these experiments,<sup>1</sup> a slight advantage is gained by warming the tubes in a water-bath at 37° C. for *five to ten minutes*, before the addition of hemolysin and corpuscles. As shown in Tables III and IV some sera show stronger reactions with the *smaller amounts* in tests conducted by giving the brief preliminary warming than in tests to which the hemolysin and corpuscles are added to the cold tubes. A preliminary warming of five minutes is almost as good as fifteen minutes; thirty minutes introduces more of the nonspecific factors and for these reasons we believe that *the period of preliminary warming, if used at all, should not be less than five or more than fifteen minutes.*

TABLE IV  
SECONDARY INCUBATION AT 38° C. VERSUS SECONDARY INCUBATION AT 38° C. AFTER  
PRELIMINARY WARMING OF TUBES FOR TEN MINUTES

NO.	HEMOLYSIN AND CORPUSCLES ADDED TO COLD TUBES; SECONDARY INCUBATION AT 38° C.						TUBES PLACED IN WATER-BATH FOR TEN MINUTES BEFORE ADDITION OF HEMOLYSIN AND CORPUSCLES					
	0.1	0.02	0.004	0.0008	0.00016	CONTROLS' HEMOLYSIS	0.1	0.02	0.004	0.0008	0.00016	CONTROLS' HEMOLYSIS
1	—	—	—	—	—	15 min.	—	—	—	—	—	30 min.
2	1	1	—	—	—	30 min.	2	2	2	—	—	1 hour
3	4	4	4	—	—	2 hours	4	4	4	1	—	1 hour
4	2	2	2	—	—	2 hours	4	4	4	1	—	1 hour
5	4	4	4	—	—	30 min.	4	4	4	1	—	1 hour
6	4	4	4	—	—	30 min.	4	4	4	1	—	1 hour
7	4	4	4	3	—	2 hours	4	4	4	4	—	2 hours
8	4	4	4	3	—	30 min.	4	4	4	4	—	1 hour
9	4	4	—	—	—	15 min.	4	4	2	—	—	1 hour
10	4	2	1	—	—	30 min.	4	4	1	1	—	1 hour

*A Fixed Period of Secondary Incubation versus a Variable Period for Each Serum.*—The advantages of a fixed period for the secondary incubation is one of convenience when testing a large number of sera, inasmuch as inspection of serum controls and removal of

the tubes when complete hemolysis has taken place, may not be a practical method by reason of the time and labor involved.

The advantage, however, of the variable period for individual sera is a check upon the possible influence of natural hemolysins when tests are being conducted with an antisheep or an antiox hemolytic system. Sera containing large amounts of natural hemolysin may yield somewhat weaker reactions with a fixed period of secondary incubation than with a variable period in which the tests are concluded and the reactions read as soon as the controls are completely hemolyzed. This fact is shown in the results of a few reactions from a series of tests given in Table V; the variable period of secondary incubation tends to yield somewhat more sensitive reactions when the tests are conducted with an antisheep hemolytic system.

TABLE V  
INFLUENCE OF METHOD OF SECONDARY INCUBATION UPON THE RESULTS OF COMPLEMENT-FIXATION TESTS CONDUCTED WITH AN ANTISHEEP SYSTEM

NO.	WATER-BATH 1 HOUR, READINGS 2 HOURS LATER					WATER-BATH UNTIL CONTROLS WERE HEMOLYZED, READINGS 2 HOURS LATER					
	0.1	0.02	0.004	0.0008	CONTROL	HEMOLYSIS OF SERUM CONTROLS	0.1	0.02	0.004	0.0008	CONTROL
1	3*	4	2	—	—	10 min.	4	4	3	—	—
2	4	4	—	—	—	15 "	4	4	2	—	—
3	4	4	4	—	—	25 "	4	4	4	—	—
4	4	4	3	—	—	10 "	4	4	4	—	—
5	4	4	3	—	—	17 "	4	4	3	—	—
6	4	4	—	—	—	25 "	4	4	—	—	—

\*4 equals ++++; 3 equals +++; 2 equals ++; 1 equals +.

As shown in Table VIII these differences are not apparent when the tests are conducted with an antihuman system, because of the absence of the influence of natural hemolysins.

However, the slight advantage to be gained by the variable method of secondary incubation is offset not so much by the greater time and labor involved, but rather by the danger of falsely positive reactions. When the serum, antigen and hemolytic controls show just complete hemolysis there may be in the mixtures of serum and antigen, very slight inhibition of hemolysis which will disappear with a longer period of incubation. If the readings are made, how-

ever, when the controls just show complete hemolysis, these weak inhibitions of hemolysis in the main tubes may be erroneously interpreted as weakly positive reactions.

## Part 2

### TIME OF READING REACTIONS

As previously stated, many serologists place the tubes in a refrigerator overnight before the readings are made, which facilitates the readings and constitutes a distinct advantage.

In our experience<sup>3</sup> this practice may lead to a small percentage of falsely negative reactions with weakly positive sera tested with an antish sheep hemolytic system, due to the presence of natural hemolysins in some sera; if the readings are made within two or three hours after the completion of the secondary incubation, the influence of an excess of hemolysin is greatly reduced and indeed, may be rendered inactive by heating the tubes in a water-bath at 55° C. for ten minutes.<sup>4</sup>

Table VI gives the results of complement-fixation tests with a few of a series of sera tested in duplicate; the primary incubation for

TABLE VI  
INFLUENCE OF METHODS OF SECONDARY INCUBATION AND READING UPON THE RESULTS OF COMPLEMENT-FIXATION TESTS WITH ANTISHEEP SYSTEM

NO.	WATER-BATH 1 HOUR READINGS NEXT DAY						WATER-BATH UNTIL HEMOLYSIS OF CON- TROLS, READINGS AT ONCE							
	0.1	0.02	0.004	0.0008	0.00016	CONTROL	HEMO- LYSIS OF CONTROL	*	0.1	0.02	0.004	0.0008	0.00016	CONTROL
1	3*	3	1	—	—	—	25 min.	3	3	2	1	—	—	—
2	3	3	—	—	—	—	15 "	4	4	1	1	—	—	—
3	3	3	1	—	—	—	58 "	4	4	3	—	—	—	—
4	4	3	—	—	—	—	22 "	4	4	1	1	1	—	—
5	4	4	3	1	—	—	23 "	4	4	4	3	1	—	—
6	4	4	1	—	—	—	30 "	4	4	1	—	—	—	—
7	4	4	3	—	—	—	24 "	4	4	3	1	1	—	—
8	4	4	3	1	—	—	23 "	4	4	3	1	1	—	—
9	4	3	—	—	—	—	50 "	4	3	1	—	—	—	—
10	4	4	—	—	—	—	15 "	4	4	2	—	—	—	—
11	2	1	—	—	—	—	23 "	3	3	1	—	—	—	—
12	1	1	—	—	—	—	30 "	2	1	1	—	—	—	—

\*4 equals + + + +; 3 equals + + +; 2 equals + +; 1 equals +.



both was eighteen hours at 8° C. With both sets the hemolysin and corpuscles were added to the cold tubes and one set placed in a water-bath for one hour and then in a refrigerator, the readings being made the next day, while the second set was placed in the same water-bath and the tubes removed after complete hemolysis of the hemolytic, antigen and serum controls and the readings made at once. With practically every serum the latter method showed stronger reactions. As shown in this table, the majority of serum controls were completely hemolyzed in much less than one hour.

Table VII gives the results of similar experiments in which each serum was tested in three ways as follows: (1) With a secondary

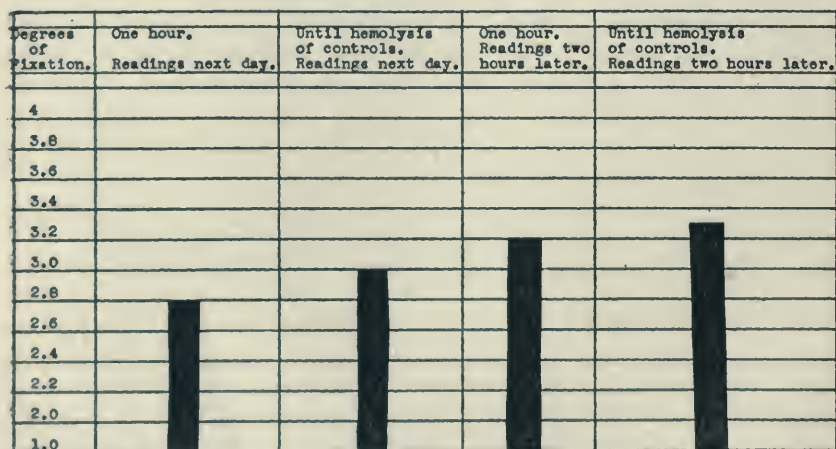


Chart 1.

incubation in a water-bath for one hour and readings after standing in the refrigerator overnight; (2) with a secondary incubation until the controls were hemolyzed and readings two hours later and (3) readings of set No. 2 after standing in a refrigerator overnight.

As shown in this table the controls of all sera were completely hemolyzed in about one half hour; the set incubated until the hemolysis of the controls and read two hours later yielded the most sensitive reactions. The set incubated until the hemolysis of the controls and read next day yielded slightly more sensitive reactions with some sera than the set incubated for a fixed period of one hour and read next day.

TABLE VII  
INFLUENCE OF METHODS OF SECONDARY INCUBATION AND READING UPON THE RESULTS OF COMPLEMENT-FIXATION TESTS WITH  
ANTSHEEP SYSTEM

NO.	WATER-BATH 1 HOUR READINGS NEXT DAY					WATER-BATH UNTIL CONTROLS WERE HEMOLYZED READINGS NEXT DAY					WATER-BATH UNTIL CONTROLS WERE HEMOLYZED READINGS 2 HOURS LATER					
	0.1	0.02	0.004	0.0008	CONTROL	HEMOLYSIS OF SERUM CONTROLS	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL
1	1*	2	1	—	—	25 min.	1	3	1	—	—	4	4	3	—	—
2	4	3	1	—	—	25 min.	4	4	4	—	—	4	4	4	3	—
3	4	4	4	—	—	25 min.	3	4	4	—	—	4	4	4	1	—
4	3	4	4	3	—	25 min.	4	4	4	2	—	4	4	4	4	—
5	4	4	4	1	—	25 min.	4	4	4	—	—	4	4	4	1	—
6	4	4	4	1	—	35 min.	3	4	4	—	—	4	4	4	4	—
7	4	4	4	3	—	35 min.	4	4	4	3	—	4	4	4	4	—
8	4	4	4	2	—	30 min.	4	4	4	3	—	4	4	4	4	—
9	4	4	4	4	—	25 min.	4	4	4	2	—	4	4	4	3	—
10	4	4	4	4	—	25 min.	4	4	4	—	—	4	4	4	4	—
11	1	2	—	—	—	35 min.	1	2	—	—	—	3	4	1	—	—
12	3	4	2	—	—	30 min.	3	4	3	—	—	4	3	3	—	—

\*4 equals + + + + +; 3 equals + + + +; 2 equals + +; 1 equals +.

TABLE VIII  
INFLUENCE OF METHODS OF SECONDARY INCUBATION AND READING UPON RESULTS OF COMPLEMENT FIXATION WITH  
ANTHUMAN SYSTEM

NO.	PRIMARY INCUBATION 1 HOUR SECONDARY INCUBATION 1 HOUR READINGS NEXT DAY					PRIMARY INCUBATION 18 HOURS SECONDARY INCUBATION 1 HOUR READINGS 2 HOURS LATER					PRIMARY INCUBATION 18 HOURS SECONDARY INCUBATION 1 HOUR READINGS NEXT DAY					PRIMARY INCUBATION 18 HOURS SECONDARY INCUBATION UNTIL HEMO- LYSIS OF CONTROLS READINGS TWO HOURS LATER				
	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL
1	—	—	—	—	—	4	—	—	—	—	4	—	—	—	—	4	1	—	—	—
2	—	—	—	—	—	4	—	—	—	—	4	—	—	—	—	4	1	—	—	—
3	—	—	—	—	—	4	1	—	—	—	4	—	—	—	—	4	4	—	—	—
4	—	—	—	—	—	3	—	—	—	—	3	—	—	—	—	4	—	—	—	—
5	1	—	—	—	—	4	—	—	—	—	4	—	—	—	—	4	1	—	—	—
6	4	—	—	—	—	4	4	1	—	—	4	4	1	—	—	4	4	4	—	—
7	4	—	—	—	—	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
8	—	—	—	—	—	4	1	—	—	—	4	1	—	—	—	4	4	—	—	—
9	2	—	—	—	—	4	1	—	—	—	4	1	—	—	—	4	3	—	—	—
10	3	—	—	—	—	4	2	—	—	—	4	2	—	—	—	4	4	—	—	—

\*Time for hemolysis of antigen control was fifteen minutes; f for hemolytic control twelve minutes.



A summary of experiments of this character is given in Chart 1. Only known syphilitic sera were used and four sets of tests conducted with each serum at the same time, with the same antigen and same hemolytic system. The primary incubation for all was eighteen hours at 8° C. and hemolysin and corpuscles were added to the cold tubes. The first set was given a secondary incubation in a water-bath at 38° C. for one hour and the readings made after the tubes had stood in a refrigerator at 6° C. overnight; the second set was the same except that the readings were made after the tubes had stood at room temperature (20°-22° C.) for two hours; the third set was incubated until hemolysis of the controls (about thirty minutes) and the reactions read after the tubes had been placed in a refrigerator overnight; the fourth set was conducted in the same manner except that the readings were made after the tubes had stood at room temperature for two hours.

The strongest reactions were observed in the set incubated until hemolysis of the controls and readings two hours later; almost the same results were obtained with the set incubated for one hour and read two hours later; slightly weaker reactions were observed with the set incubated until hemolysis of the controls and read next day and still weaker reactions with the set incubated for one hour and read next day. *The differences however, in the strength of the reactions were slight and usually only apparent with the smaller amounts of serum;* as shown in the tables the 0.1 c.c. amount of serum occasionally yielded a weaker reaction than the 0.02 c.c. amount, due in part to the influence of natural antisheep hemolysin.

With an antihuman hemolytic system these differences in reactions depending upon the duration of secondary incubation and time of readings, are not nearly so apparent or important. The results of comparative tests with a few of a series of sera are shown in Table VIII; sets incubated one hour and read next day have yielded reactions almost identical with those incubated until hemolysis of the controls and read two hours later.

#### SUMMARY

1. The kind and temperature of the incubator employed for the secondary incubation in complement-fixation tests has an important influence on the reactions.

2. Water-bath incubation at 37° C. facilitates hemolysis better than an air incubator at the same temperature and from the standpoint of economy in time is to be preferred.

3. Air incubation, however, occasionally results in stronger reactions than the water-bath due in part to the time allowed for the fixation of complement by syphilitic serum and tissue extract before hemolysis occurs.

4. Secondary incubation in a water-bath at 30° C. occasionally yields stronger reactions than at 40° C. The lower temperatures of incubation may, however, result in incomplete hemolysis of the controls; the optimum temperature for a water-bath is from 35° to 38° C. with an average of 37° C.

5. With a primary incubation of eighteen hours at 8° C., warming the tubes in a water-bath at 37° C. for five to fifteen minutes (not longer) before the addition of hemolysin and corpuscles, occasionally results in stronger reactions than when hemolysin and cells are added to the cold tubes. A longer period of warming is frequently unsatisfactory due to increased nonspecific fixation of complement by serum or tissue extract.

6. With the antisheep and antiox hemolytic systems the most delicate reactions are observed when the results with each serum are read immediately after complete hemolysis of the antigen, hemolytic and individual serum controls. Next in order of sensitiveness are reactions read immediately after an arbitrary period of secondary incubation of one hour. An arbitrary period of secondary incubation of one hour followed by placing the tubes in a refrigerator overnight before reading the reactions, occasionally results in weaker reactions and even falsely negative reactions with weakly positive sera unless special precautions are taken as described elsewhere.<sup>4</sup>

#### CONCLUSIONS

1. The water-bath at 37° C. is best adapted for conducting the secondary incubation in complement-fixation tests.

2. With a primary incubation of eighteen hours at 8° C. it is advisable to warm the tubes in a water-bath at 37° C. for five to fifteen minutes (not longer) followed by the addition of hemolysin and corpuscles and secondary incubation of one hour.

3. Reactions read after the tubes have stood in a refrigerator for two or three hours for the partial settling of corpuscles are frequently more delicate than readings made the following day and practically the same as readings made immediately after hemolysis of the controls.

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STUDIES IN THE STANDARDIZATION OF THE  
WASSERMANN REACTION. XXII\*

A METHOD FOR PREVENTING THE INFLUENCE OF NATURAL ANTISHEEP  
HEMOLYSIN UPON COMPLEMENT-FIXATION REACTIONS  
AFTER THE SECONDARY INCUBATION

BY JOHN A. KOLMER, M.D., PHILADELPHIA, PA.

*From the Dermatological Research Institute of Philadelphia*

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THE influence of natural antisheep hemolysins in human sera upon complement-fixation reactions can be prevented by close adjustment of the hemolytic system to avoid an excess of complement<sup>1, 2, 3</sup> and by reading the reactions within an hour or two after completion of the secondary incubation.

If however, the tubes are placed in a refrigerator overnight for the settling of corpuscles in order to facilitate the readings, a slight degree of hemolysis may occur with those sera containing exceptionally large amounts of natural hemolysin; *the method described in this article has been found a means of preventing this hemolysis and consists in placing the tubes in a water-bath at 55° C. for ten minutes immediately after the secondary incubation.* This period of heating destroys complement and thereby breaks up the hemolytic system; tubes placed in a refrigerator for twenty-four hours after heating at 55° C. for ten minutes yield readings practically identical with those observed by centrifuging the tubes immediately after the period of secondary incubation.

As is well known complement is highly thermolabile; in our tests the complement serum is diluted 1:30 and heating in a water-bath at 55° C. for ten minutes always results in total destruction of hemolytic activity, as shown in Table I; this is likewise true of complement diluted 1:20. Some complement sera diluted 1:10 may show a trace of hemolytic activity after heating at 55° C. for ten minutes; however, since the diluted complement is still further

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\*Investigation aided by funds accruing from the preparation of arsphenamine.

diluted by antigen, serum, corpuscle suspension and saline solution in complement-fixation tests, heating tubes for ten minutes at 55° C. after the secondary incubation serves for the destruction of complement in the original Wassermann test.

TABLE I

THE INFLUENCE OF HEATING AT 55° C. IN A WATER-BATH UPON THE HEMOLYTIC ACTIVITY OF GUINEA PIG COMPLEMENT DILUTED 1:30

COMPLEMENT	UNITS	
	NO. 1	NO. 2
Unheated.....	0.2	0.25
Heated for 1 minute.....	0.2	0.25
Heated for 3 minutes.....	0.2	0.3
Heated for 5 minutes.....	0.25	0.4
Heated for 10 minutes.....	0.4	0.8
Heated for 15 minutes.....	—*	—*

\*No unit in 1 c.c.

Experiments have shown that hemolysis in mixtures of complement, hemolysin and corpuscles may be promptly inhibited by heating the tubes at 55° C.; this means that complement already united to hemolytic amboceptors and corpuscles may be destroyed by heating in a water-bath at this temperature.

Natural antisheep hemolysin, however, is largely thermostabile;<sup>4</sup> likewise rabbit immune hemolysin. Heating at 55° C. for ten minutes has therefore, slight or no influence upon antisheep hemolysin and hemolysis is prevented by destruction of complement.

*Five per cent suspensions of washed fresh sheep corpuscles may be heated in a water-bath at 55° C. for ten minutes without producing hemolysis; with an exposure of fifteen to thirty minutes very slight hemolysis may be produced.* For this reason the tubes should not be heated for longer than ten minutes as this suffices for the destruction of complement without breaking up fresh corpuscles (preserved corpuscles are more susceptible to heat).

A large series of comparative complement-fixation tests in which each serum was tested by placing one set of reactions in a refrigerator overnight immediately after the secondary incubation and a second set after heating the tubes in a water-bath at 55° C. for ten minutes after the secondary incubation followed by settling the

corpuscles in a refrigerator overnight, have shown that hemolysis does not continue with the latter technic and the readings next day are practically identical with those observed immediately after the secondary period of incubation.

Table II gives the results of a few comparative tests from a series conducted with an antisheep system in which the complement was used in a constant dose of 1 c.c. of 1:20 dilution with two units of hemolysin, three different antigens and 0.2 c.c. of serum.

TABLE II  
THE INFLUENCE UPON COMPLEMENT-FIXATION REACTIONS OF HEATING THE TUBES  
IN A WATER-BATH AT 55° C. FOR TEN MINUTES AFTER THE  
SECONDARY INCUBATION

SERA	NOT HEATED *				HEATED AFTER SECONDARY INCUBATION *			
	C. B. H. **	S	A	CONTROL	C. B. H.	S	A	CONTROL
1	++++	+	+	—	++++	++	++	—
2	++	—	—	—	+++	+	+	—
3	++++	++	++++	—	++++	++	++++	—
4	++++	++	++++	—	++++	++	++++	—
5	++	—	+	—	++	+	+	—
6	++	—	+	—	++	+	+	—
7	++++	++	++	—	++++	++	++	—
8	++++	+	+++	—	++++	++	++++	—

\*Reading made twenty-four hours after secondary incubation.

\*\*C. B. H. equals cholesterolized beef heart extract; S equals alc. syphilitic liver;  
A equals acetone insoluble lipoids.

Tables III and IV give the results of a few tests from a series in which the sera were tested in graded amounts with two units of complement diluted 1:30 and four units of hemolysin.

As shown in these tables, heating the tubes in a water-bath at 55° C. for ten minutes after the secondary incubation and reading the results next day resulted in stronger reactions with numerous sera than occurred with duplicate sets in which this period of heating was omitted. Of course not every serum showed these differences, but only those containing relatively large amounts of natural antisheep hemolysin.

The method can be recommended as a simple and efficient means for preventing continued hemolysis after the secondary incubation, when the readings are to be made after the tubes have been kept in a refrigerator overnight.



TABLE III  
THE INFLUENCE UPON COMPLEMENT-FIXATION REACTIONS OF HEATING THE TUBES IN A WATER-BATH AT 55° C. FOR TEN MINUTES AFTER THE SECONDARY INCUBATION

SERA	NOT HEATED*						HEATED AFTER SECONDARY INCUBATION*					
	0.1	0.02	0.004	0.0008	0.00016	CONTROL	0.1	0.02	0.004	0.0008	0.00016	CONTROL
1	-	-	-	-	-	-	+	-	-	-	-	-
2	++	++	-	-	-	-	++	++	++	-	-	-
3	++	++	-	-	-	-	++	++	++	-	-	-
4	++	++	-	-	-	-	++	++	++	-	-	-
5	++	++	-	-	-	-	++	++	++	-	-	-
6	++	++	-	-	-	-	++	++	++	-	-	-
7	++	++	-	-	-	-	++	++	++	-	-	-
8	++	++	-	-	-	-	++	++	++	-	-	-
9	++	++	-	-	-	-	++	++	++	-	-	-
10	++	++	-	-	-	-	++	++	++	-	-	-
11	++	++	-	-	-	-	++	++	++	-	-	-
12	++	++	-	-	-	-	++	++	++	-	-	-

\*Readings made after the tubes had been in a refrigerator for twenty-four hours after the secondary incubation.

TABLE IV  
THE INFLUENCE OF HEATING AT 55° C. FOR TEN MINUTES AFTER THE SECONDARY INCUBATION\*

NO.	UNHEATED READINGS TWO HOURS AFTER					UNHEATED READINGS NEXT DAY					HEATED READINGS NEXT DAY				
	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL	0.1	0.02	0.004	0.0008	CONTROL
1	4	4	3	—	—	4	4	3	—	—	4	4	3	—	—
2	4	4	2	—	—	4	3	1	—	—	4	3	2	—	—
3	4	4	3	—	—	4	4	3	—	—	4	4	3	—	—
4	4	4	4	4	—	4	4	4	2	—	4	4	4	3	—
5	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
6	4	4	3	1	—	4	2	—	—	—	4	4	3	1	—
7	4	4	—	—	—	4	4	—	—	—	4	3	—	—	—
8	4	4	3	3	—	4	4	3	1	—	4	4	3	3	—
9	2	2	—	—	—	4	1	—	—	—	4	2	—	—	—
10	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
11	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
12	4	4	—	—	—	4	4	—	—	—	4	4	—	—	—
13	4	4	—	—	—	4	4	—	—	—	4	4	3	—	—
14	4	4	4	—	—	4	4	2	—	—	4	4	4	—	—
15	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—
16	4	4	4	—	—	4	4	4	—	—	4	4	4	—	—

\*Antisheep hemolytic system; primary incubation eighteen hours at 8° C.; secondary incubation one hour in water-bath at 37° C.

## CONCLUSIONS

1. The influence upon complement-fixation reactions after the secondary incubation of an excess of antisheep hemolysin represented by natural hemolysin in human sera, may be prevented by heating the tubes in a water-bath at 55° C. for ten minutes.

2. This period of heating prevents further hemolysis by the destruction of complement which thereby breaks up the hemolytic system.

3. Heating in a water-bath at 55° C. for ten minutes does not cause the hemolysis of sheep corpuscles.

4. The reactions observed after heating the tubes for 10 minutes at 55° C. after the secondary incubation followed by settling in a refrigerator until next day, are practically identical with the reactions immediately after the secondary period of incubation.

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# A STUDY OF THE RELATION BETWEEN SYPHILIS AND DIABETES MELLITUS

BY JACOB ROSENBLOOM, M.D., PH.D., PITTSBURGH, PA.

## I. REVIEW OF THE LITERATURE

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THE recent work of Warthin and Wilson<sup>1</sup> has stimulated interest in the coincidence of latent syphilis and diabetes. They report that in six necropsies in cases of diabetes, all presented histologic changes of syphilis; in four of them spirochetes were found in the myocardium, and in one of these cases in the pancreatic lesions. They also report that the pancreas in forty-one cases of latent syphilis already reported by Warthin<sup>2</sup> showed marked changes, and conclude that "latent syphilis" is the chief factor in the production of the form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of this type of pancreatitis.

For several years, I have been interested in the possible relationships between clinically demonstrable syphilis and diabetes, and have studied the cases of diabetes encountered in practice in regard to this relationship. The data are presented in this paper.

It is quite possible that syphilis might cause diabetes by producing a specific lesion of the brain, especially of the medulla. Syphilitic arterial disease with secondary nervous lesions in the region of the fourth ventricle, or a gumma in this part would also be capable of producing diabetes. Again, syphilis might produce diabetes by causing disease of the blood vessels of the pancreas and secondary disease of pancreatic gland tissue.

Von Noorden<sup>3</sup> mentions cases of glycosuria reported to have been cured by treatment with mercury and iodids.

F. Hirschfeld<sup>4</sup> found that 6 per cent of his cases of diabetes could be claimed to be on a syphilitic basis. Von Noorden<sup>5</sup> discovered 1.2 per cent of male diabetics under 20 years, were syphilitic, 7.1 per cent of male diabetics over 20 years, and 2.3 per cent of female diabetics,

of various ages. Sarra's<sup>6</sup> statistics are about the same. Scheinmann,<sup>7</sup> Neumann,<sup>8</sup> Ehrmann<sup>9</sup> and Lombroso<sup>10</sup> have also published reports on the relation between diabetes and syphilis.

Ord<sup>11</sup> has recorded several cases in which glycosuria has been found in patients presenting the ordinary general symptoms of constitutional syphilis.

Feinberg<sup>12</sup> has reported three cases of diabetes and one of glycosuria which were apparently of syphilitic origin. These were all cases of nerve involvement and were under antisymphilitic treatment; recovery occurred in one of the cases, improvement in the other two, but in the case of glycosuria no definite improvement followed.

Williamson,<sup>13</sup> in 100 cases of diabetes, obtained a history or indication of previous syphilis in six cases, and found in these no reason to regard syphilis as the cause of the diabetes. Walker and Haller<sup>14</sup> reported seven positive Wassermann reactions in eighty-nine cases of diabetes, and obtained a history of syphilitic infection in a majority of these seven cases.

Laurent<sup>15</sup> has described a case of diabetes in a syphilitic cured by mercury. Carnot and Harvier<sup>16</sup> give a clinical and postmortem report of a case of diabetes in a syphilitic due to gummosis lesions of the pancreas. The subject, a woman of 53, had shown symptoms of neurosyphilis and diabetes for about two years. The urine had been abundant and had contained from 66 to 72 gms. of sugar per liter. Death was due to pneumonia. The pancreas was found to be transformed almost entirely into a sclerogummatous mass. The authors regard this as the first reported case of diabetic manifestation due unquestionably to syphilitic lesions of the pancreas. Four other cases from the literature are cited but in these autopsy showed only ordinary sclerosis of the pancreas.

Simmonds<sup>17</sup> made a postmortem examination in 300 cases of diabetes. In 20 cases syphilis was found, but only in three cases did there exist syphilitic changes of the pancreas.

Janeway<sup>18</sup> has described a case of syphilis and diabetes. Padilla and Paz<sup>19</sup> report three new cases and the outcome in three cases previously published, in all of which diabetes had developed on a basis of syphilis. They found that the sugar disappeared completely from the urine of all these cases under specific treatment.

One man did not complete the course and the glycosuria returned after a primary improvement.

Ureche and Vatianu<sup>20</sup> record a case of tabes in a man aged 43, associated with paralysis of the external rectus, paralysis of the three branches of the trigeminal, and glycosuria. Treatment by mercury and salvarsan was instituted, but was without benefit. After two months' treatment the paralysis became more marked and the oculomotor nerve became affected. The glycosuria, however, disappeared; it was probably caused either by a lesion of Claude Bernard's area or by a patch of meningitis in the interpeduncular space.

Cordier and Dechaume<sup>21</sup> presented an original article on syphilitic diabetes and glycosuria of the tertiary period. They describe the various clinical types of diabetes that may be attributed to syphilis. In the secondary stage a mild and transitory glycosuria is occasionally observed. In the tertiary stage various forms appear: (1) a form associated with some cerebral lesion; (2) a form associated with lesions of the pancreas; (3) a type which is apparently independent of any cerebral or pancreatic lesion. In addition to the above, diabetes has been found in association with parasymphilis and hereditary syphilis. The characteristics of the different forms of diabetes are given, together with a very complete summary of previous observations on the subject. Various conditions should be satisfied before a case of diabetes is put down to syphilis: (1) the appearance of the diabetes should be subsequent to the infection with syphilis; (2) it should appear at the same time as other syphilitic manifestations; (3) antisymphilitic treatment should cure the diabetes as well as the other lesions; (4) antidiabetic treatment should be without effect. These conditions are not absolute and vary in importance as indications of the true nature of the diabetes. Indeed, according to Troller, the fourth condition is valueless, since all varieties of diabetes are to some extent improved by general treatment. The results of treatment in cases of diabetes due to syphilis are very encouraging. Large doses of arsenical compounds should, however, be avoided. The authors suggest that syphilis is the probable explanation of those curious cases of diabetes occurring in husband and wife, an association which has given rise to a hypothesis of a diabetes that is infectious in origin. In a series of 516 diabetics collected by Senator the



husband or wife, as the case may be, developed diabetes subsequently in 18 cases (3.5 per cent). No particular attention was paid to a history of syphilis, and it is possible that a careful investigation along such lines would have revealed the explanation of this conjugal diabetes. At any rate, the possibility of syphilis should always be kept in mind when dealing with such cases.

Revillet<sup>22</sup> has reported a cure with mercury in a case of syphilitic diabetes. Joslin<sup>23</sup> has found the Wassermann test positive six times in one hundred and seven of his cases of diabetes. Mitchell<sup>24</sup> has reported a case of diabetes associated with syphilis not helped by specific treatment, which he thinks is due to the fibrous changes present in the pancreas.

Beguier<sup>25</sup> thinks that a combination of diabetes and syphilis is frequently seen but that syphilitic diabetes is extremely rare and that there are very few cases in the literature of diabetes caused by syphilitic sclerosis of the pancreas. The author first gives a review of the literature on the subject, referring frequently to the "islets of Langerhans," and reports a case himself of a diabetic woman in whom complete sclerosis of the pancreas was found at autopsy. This case does not appear very convincing. The syphilitic infection was not definitely proved; the Wassermann test in blood and cerebrospinal fluid was negative, and infection was denied. The pancreas was not examined histologically, or at least no report of a histologic picture is given, and the diabetes, as described by the author, was certainly not a classic case.

Schulte<sup>26</sup> and Troller<sup>27</sup> also discuss the incidence of syphilis and diabetes. Leudet<sup>28</sup> in 1860 described a case of a 32-year old woman who four years previously developed a saddle nose from syphilis. She developed suddenly all the symptoms of diabetes which subsided under specific treatment. Frerichs<sup>29</sup> reported three cases of syphilis with brain symptoms and diabetes, in which the diabetes disappeared under specific treatment and in one case improved considerably.

Other similar cases are reported by Dub<sup>30</sup> and by Lemonier.<sup>31</sup> Hemptenmacher<sup>32</sup> reported a case in a 42-year old woman who had been infected with syphilis thirteen years previously. She developed symptoms of diabetes with 3.6 per cent of sugar in the urine. Under specific treatment the glycosuria disappeared without the retention of a diabetic regime. Manchot<sup>33</sup> has also described an

interesting case. Leuret and Secousse<sup>34</sup> and Reumont<sup>35</sup> describe cases of diabetes associated with gumma of pancreas. Bouchard<sup>36</sup> concludes that there exist cases of glycosuria and diabetes that begin after a luetic infection, in the secondary or tertiary stages, and finds that there are cases of diabetes improved or cured by antiluetic treatment. Richards<sup>37</sup> has studied the Wassermann reaction in diabetes with special reference to its relation to acidosis. Lebar,<sup>38</sup> Comby<sup>39</sup> and Sincard<sup>40</sup> have studied the possible effect of syphilis on the development of diabetes mellitus.

Pinard and Vielnot<sup>41</sup> in 1,000 miscellaneous cases found twenty-three with glycosuria or diabetes, and of this number fifteen had contracted syphilis, or were heredosyphilitics. This frequency of a syphilitic factor will explain certain symptoms common in diabetes, as areflexia, ocular paralyses, and monoplegias.

Bullrich<sup>42</sup> comments on the relative frequency of inherited or acquired syphilitic disease of the pancreas as a cause of diabetes. At the same time, he points out that diabetes is extremely rare among the less well-to-do although syphilis is so common among them.

Castronuova<sup>43</sup> maintains that among the causes and contributory factors of diabetes special importance should be attached to the immediate and late effects of infectious diseases, especially the latent forms of malaria, tuberculosis, and syphilis.

Lemann,<sup>44</sup> from a careful study of the relation between syphilis and diabetes concludes that there is no relation between the two diseases as regards their etiology.

Van Saun<sup>45</sup> studied the Wassermann reaction in 72 diabetics—52 gave a negative reaction, 2 doubtful reaction and in 19 cases the controls failed to hemolyze. The one positive case occurred in a patient giving a history of syphilis. Of the 2 doubtful reactions, 1 was a patient with a history of chancre twenty-six years previously, the other gave no history of syphilis.

## II. EXPERIMENTAL

This paper contains a study as to the presence of signs of syphilis in one hundred and thirty-nine cases of diabetes mellitus. Sixteen of these cases presented a positive Wassermann test, a percentage of over twelve. Eight of these cases presented signs of arteriosclerosis. It is possible that these eight cases of diabetes are syphilitic in nature, and as a part of the arteriosclerosis there would undoubtedly be present some fibrosis of the pancreas.

These eight cases were subjected to intensive treatment for the syphilis but there was no increase in their tolerance for carbohydrates after the treatment. This is no doubt due to the fact that the pancreatic fibrosis still exists after the treatment.

We may conclude therefore that in this series studied sixteen cases presented positive Wassermann tests. In about six per cent of the cases studied the diabetes existed as a part of the syphilitic process and in about six per cent the syphilis and diabetes existed as independent conditions.

TABLE I

RESULTS OBTAINED IN A STUDY OF ONE HUNDRED AND THIRTY-NINE CASES OF DIABETES MELLITUS IN RELATION TO A POSSIBLE EXISTING SYPHILIS

CASE NO.	SEX	AGE	AGE WHEN DIABETES WAS DISCOVERED	WASSERMANN TEST	CONSTITUTIONAL SIGNS OF SYPHILIS
1	Female	21	20	Negative	Absent
2	Female	46	44	Negative	Absent
3	Female	50	40	Negative	Absent
4	Female	26	23	Negative	Absent
5	Male	50	46	Negative	Absent
6	Male	44	44	Positive	Syphilitic myelitis
7	Female	56	53	Positive	Husband syphilitic
8	Female	60	52	Negative	Absent
9	Male	49	48	Negative	Absent
10	Female	60	57	Negative	Absent
11	Female	53	49	Negative	Absent
12	Male	50	45	Positive	Enlargement of liver and spleen
13	Male	49	48	Negative	Absent
14	Male	69	65	Negative	Absent
15	Male	48	44	Negative	Absent
16	Male	62	58	Positive	Aortic sclerosis
17	Female	45	43	Negative	Absent
18	Female	70	60	Negative	Absent
19	Male	45	45	Positive	History of chancre
20	Male	60	50	Negative	Wife (absent) diabetic
21	Female	38	38	Negative	Absent
22	Male	45	44	Negative	Absent
23	Female	46	43	Negative	Absent
24	Female	48	48	Negative	Absent
25	Male	58	44	Negative	Absent
26	Male	69	67	Negative	Absent
27	Female	58	54	Negative	Absent
28	Male	44	41	Negative	Absent
29	Female	48	46	Negative	Absent
30	Male	50	43	Negative	Absent
31	Male	54	52	Negative	Absent
32	Female	36	35	Negative	Absent
33	Male	43	40	Negative	Absent
34	Female	68	66	Negative	Absent



TABLE I—CONTINUED

CASE NO.	SEX	AGE	AGE WHEN DIABETES WAS DISCOVERED	WASSERMANN TEST	CONSTITUTIONAL SIGNS OF SYPHILIS
35	Male	41	39	Negative	Absent
36	Female	55	53	Negative	Absent
37	Female	43	41	Negative	Absent
38	Male	46	45	Negative	Absent
39	Male	42	41	Negative	Absent
40	Male	62	56	Negative	Absent
41	Female	55	52	Negative	Husband (absent) diabetic
42	Male	58	57	Negative	Absent
43	Female	25	22	Negative	Absent
44	Female	55	51	Negative	Absent
45	Male	45	44	Negative	Absent
46	Female	64	63	Negative	Absent
47	Male	60	54	Negative	Absent
48	Male	62	52	Negative	Absent
49	Female	59	56	Negative	Absent
50	Male	31	28	Negative	Absent
51	Female	47	46	Negative	Absent
52	Male	60	55	Negative	Absent
53	Male	55	53	Negative	Absent
54	Female	62	52	Negative	Absent
55	Male	33	31	Negative	Absent
56	Male	39	38	Negative	Absent
57	Male	52	44	Negative	Absent
58	Male	60	52	Negative	Absent
59	Male	51	49	Positive	Cardiosclerosis
60	Female	52	49	Negative	Absent
61	Male	54	44	Negative	Absent
62	Male	38	36	Positive	History of chancre
63	Male	69	67	Negative	Absent
64	Male	44	44	Negative	Absent
65	Female	58	55	Negative	Absent
66	Male	57	57	Negative	Absent
67	Male	48	48	Negative	Absent
68	Male	57	50	Negative	Absent
69	Male	47	47	Negative	Absent
70	Male	54	51	Negative	Absent
71	Female	36	35	Negative	Absent
72	Male	43	40	Negative	Absent
73	Male	45	45	Negative	Absent
74	Female	68	66	Positive	Cardiosclerosis
75	Female	40	40	Negative	Absent
76	Male	41	39	Negative	Absent
77	Male	74	67	Negative	Absent
78	Female	55	52	Negative	Absent
79	Male	52	52	Negative	Absent
80	Female	43	40	Negative	Absent
81	Male	58	58	Positive	Aortitis
82	Male	32	32	Negative	Absent
83	Male	46	43	Negative	Absent
84	Female	63	63	Positive	Cardiorenal sclerosis
85	Male	46	46	Negative	Absent
86	Female	68	68	Negative	Absent

TABLE I—CONTINUED

CASE NO.	SEX	AGE	AGE WHEN DIABETES WAS DISCOVERED	WASSERMANN TEST	CONSTITUTIONAL SIGNS OF SYPHILIS
87	Female	50	42	Negative	Absent
88	Female	33	33	Negative	Absent
89	Male	42	42	Negative	Absent
90	Male	62	56	Positive	Aortitis
91	Male	40	40	Negative	Absent
92	Female	55	52	Negative	Absent
93	Male	50	50	Negative	Absent
94	Male	57	57	Negative	Absent
95	Female	30	30	Negative	Absent
96	Female	42	40	Negative	Absent
97	Male	25	24	Negative	Absent
98	Male	35	35	Negative	Absent
99	Boy	7	6	Negative	Absent
100	Female	50	46	Positive	Aortitis
101	Male	55	55	Negative	Absent
102	Female	55	51	Negative	Absent
103	Male	53	52	Negative	Absent
104	Female	45	45	Negative	Absent
105	Female	62	62	Negative	Absent
106	Female	53	53	Negative	Absent
107	Female	56	50	Negative	Absent
108	Female	58	53	Negative	Absent
109	Female	53	51	Negative	Absent
110	Male	28	28	Negative	Absent
111	Male	33	33	Negative	Absent
112	Male	38	38	Negative	Absent
113	Female	42	42	Negative	Absent
114	Female	47	40	Negative	Absent
115	Male	60	55	Negative	Absent
116	Female	60	50	Negative	Absent
117	Female	50	48	Positive	Aortitis
118	Male	53	33	Negative	Absent
119	Male	46	45	Negative	Absent
120	Female	62	52	Negative	Absent
121	Male	33	31	Negative	Absent
122	Male	39	39	Negative	Absent
123	Female	51	47	Negative	Absent
124	Male	49	41	Negative	Absent
125	Female	56	56	Negative	Absent
126	Male	41	41	Negative	Absent
127	Male	45	45	Positive	Absent
128	Male	55	55	Positive	Absent
129	Male	49	41	Negative	Absent
130	Male	28	28	Negative	Absent
131	Female	59	59	Negative	Absent
132	Female	64	58	Negative	Absent
133	Female	52	52	Negative	Absent
134	Female	52	52	Positive	Absent
135	Male	54	54	Negative	Absent
136	Male	38	36	Negative	Absent
137	Female	66	66	Negative	Absent
138	Female	68	58	Negative	Absent
139	Female	50	48	Positive	Aortitis

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## EPITROCHLEAR ADENOPATHY IN SYPHILIS

By R. H. RULISON, M.D., NEW YORK CITY

*From the Department of Syphilology, Bellevue Hospital*

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AS THE advent of x-ray diminished the willingness and ability of the surgeon to recognize fractures on clinical findings alone, so the adoption of the Wassermann test as a criterion in the detection of syphilis has dulled our clinical acumen in diagnosing this common disease. There has been much discussion of the possible existence of special strains of the *Spirochete pallida* which have selective affinities for different structures. Much ink has dried in arguing this point, and meanwhile we are almost forgetting the undebatable fact that the causative agent of syphilis has a selective action on lymphatic tissue.

Brown and Pearce<sup>1</sup> who have done some remarkable work on rabbit syphilis during the past two years say, "Syphilographers have long recognized the existence of an affinity of *Spirochete pallida* for lymphoid tissue and the adenopathy of syphilis is one of its most characteristic features. In like manner, it has been shown that, in all lesions, the points at which the spirochetes tend to accumulate in greatest numbers are the perivascular lymphatics."

Fernet<sup>2</sup> has pointed out that the slower infections of tuberculosis and syphilis are characterized by glandular adenopathy while rapid ones like pneumonia, meningitis and others of short incubation period and fierce attack, do not show this sign.

Hunter<sup>3</sup> says, "A microorganism by growing in or passing through a gland seems to lose some of its virulence and it may be that it is this attenuation of the virus that determines the chronicity of the growth as well as the limitation of the infection to the lymphatic system."

The part played by the lymphatic system in delaying the rapid spread of the syphilitic infection is of vital importance. Highman<sup>4</sup> says: "At the moment of infection the spirochetes gain a foothold in the injured tissue, multiplying and invading the local lymphat-

ies, and rapidly entering the lymph. vessels. \* \* \* At its inception, syphilis is a disease of the lymphatics and its early avenues of dissemination are restricted to this system. If a chancre be studied histologically by the Levaditi method, the perivascular lymph spaces will be found filled with the microorganisms and here and there one of the latter will be seen penetrating the wall of a small blood vessel, thus entering the general circulation."

Ever since Ricord<sup>5</sup> made his famous statement that "adenopathy follows the chancre as the shadow the body" it has been the custom of authors and teachers to emphasize the regional adenopathy which occurs in primary syphilis. But the general adenopathy that accompanies the disease and the diagnostic significance of palpable superficial glands has failed to receive the same degree of emphasis. The explanation of this probably lies in the wide differences both in clinical observation and in interpretation of this symptom.

Montgomery<sup>6</sup> in speaking of inoculation, says: "Almost always the sole site of infection of the syphilitic virus is into the rete malpighii of the skin and mucous membranes, an organ absolutely devoid of blood vessels and rich in lymphatic spaces. Possibly nowhere in the body is there a situation more favorable for the growth of an anaerobic microorganism. It may be that the tissue immediately outside the blood vessels is approximately as favorable." This quotation is of especial interest as bearing on the fact that the syphilitic organism from the time of inoculation to the termination of the disease finds its most favorable surroundings in tissues rich in lymphatics.

In the same article Montgomery said: "All along the track pursued by the invading treponemata there must be this continual effort to invade the blood through the thin wall of the lymphatic vessels. The blood, however, so inimical to the invaders, must keep the main body in the lymphatic vessels. It would therefore seem probable that the vast mass of the treponemata which enter the blood for general distribution do so by way of the great lymphatic trunks."

The advance of the infection is delayed at every lymph node, the spirochetes being able to continue their march only after, by force of numbers, they have inundated the filtering beds of the gland. Thus the body absorbs the toxins of the microorganisms gradually

and has some little time to marshal its defenses before it is subjected to an attack in force by the entry of large numbers of spirochetes into the blood stream.

The few spirochetes which at this stage escape into the general circulation are again caught in the meshes of the lymphatic system on leaving the peripheral capillaries from which, by grace of the slow circulation and the thin walls, they again penetrate into the tissues. This filtering process goes on during the entire second incubation period and it is only after the entire lymphatic system becomes overloaded with the rapidly multiplying parasites that the secondary stage is ushered in.

The regional lymph nodes enlarge early in the primary stage. This early enlargement is, of course, due to the large numbers of organisms procreated at the site of the chancre and hurried along the lymph conductors to the nearest gland. The lymph nodes of the rest of the body are attacked much more gradually. Nevertheless, they are attacked during the primary stage and all react defensively by hyperplasia.

In the secondary stage probably all the lymph glands of the body have been the site of a losing battle, and are becoming chronically inflamed, the resultant enlargement often persisting throughout the infected individual's life. Fernet<sup>2</sup> says, "Later along with the secondary eruption numerous adenopathies appear in different parts of the body which persist as stigmata of the old infection and which are of great value in the diagnosis of latent syphilis; from this point of view the epitrochlear and suboccipital glands are noteworthy as permanent, one might say perpetual, stigmata, warranting suspicion of the specific nature of illnesses of obscure etiology."

It is generally held that all glands in the body, both superficial and deep are enlarged in syphilis. From the standpoint of diagnosis, however, adenopathy of the deep glands is not usually of great importance, and in this paper only the enlargement of readily palpable glands is under consideration. Fournier<sup>7</sup> said that the virus had a special affinity for certain groups of glands, but this does not seem entirely warranted, at least when applied to the groups he selected and in the order of preference that he chose.

The question whether certain glands or groups of glands are more definitely enlarged than others in syphilis has been answered in the



affirmative by a number of famous syphilographers. The difficulty in accepting their judgment on this point arises from the fact that no two of them seem to be in agreement as to which glands are most favored by the organism. For practical purposes it seems wise to confine our study to a gland which is seldom enlarged in conditions other than syphilis, which drains a definitely known area easily inspected, and which is not normally palpable. For this purpose the epitrochlear gland has been chosen.

The superficial glands of the body are known by different names but all of them are fairly descriptive. According to their location either singly or in groups they are spoken of as (1) the occipital, or suboccipital; (2) the postauricular, or mastoid, (3) the preauricular, or parotid; (4) the submaxillary; (5) the submental; (6) the postcervical; (7) the anterior-cervical, (8) the axillary, (9) the epitrochlear, or antecubital, and (10) the inguinal. The inguinal and the anterior cervical glands are palpable in such a large number of normal individuals that their enlargement is of little significance in differential diagnosis. The axillary glands are not readily and accurately palpable for anatomic reasons; they are really classified with the deep lymphatics. Furthermore, since the axilla is a location difficult to keep scrupulously clean, many patients do not relish their examination. The occipital gland is not really superficial since it lies just under the fascia. Although it is enlarged in many itching conditions of the scalp, it is highly valued by syphilographers since it is palpable in a large proportion of syphilities. The auricular glands are sometimes enlarged in syphilis but not constantly enough to make negative findings significant. The submaxillary and submental glands are valuable aids in the diagnosis of syphilis for they are often enlarged and palpable. They are, however, subject to the same qualification that applies to most of the other groups, namely, that they are often enlarged from other causes, for example, mouth or tooth infections, whooping cough, etc. The posterior cervical glands are included among the groups that are found diagnostically useful by most syphilographers. They are less commonly enlarged in tuberculosis than is the anterior chain. Tuberculous involvement of these glands is not, however, so uncommon as to warrant the too great emphasis of their palpability in

diagnosis, and the possibility of a combination of syphilis and tuberculosis in the same individual must be remembered.

In plague the inguinal and the axillary glands seem to be most severely attacked. In tuberculosis the most common adenopathies are found in the anterior cervical, submaxillary, inguinal and axillary regions.

In syphilis the relative importance of adenopathy is given by Friedlander as: (1) epitrochlear, (2) occipital, and (3) posterior cervical. Other observers give entirely different groups and fail to confirm the observations of those who preceded them in expressing an opinion. The matter is not a simple one to unravel.

*Note:* There is a small chain of glands draining the breast region which lies along the lower border of the pectoralis major. Some writers speak of adenopathy of these glands as strong evidence of syphilis. They were seldom observed in this series of cases. They are referred to as the pectoral glands.

The epitrochlear gland has been selected as the subject of this paper for several reasons: 1. It is in a location easy to palpate, and which does not arouse the suspicions of the patient. 2. It is not commonly enlarged. 3. When not enlarged, it is not normally palpable. 4. When enlarged it is always palpable except in obese individuals. (By this is meant, not merely extremely fat persons, but all those having a layer of subcutaneous fat thicker than the average.) 5. It belongs to a class of glands intermediate between the simple lymphatic nodule and the more highly developed and differentiated glands of the lymphatic system. (Whether or not this fact makes it a site more favored by the spirochetes than the fully developed glands is undetermined.)

*Anatomy of the Epitrochlear Gland:* Sappey<sup>8</sup> says: "The collecting lymphatic trunks, which arise from the integuments of the fingers and hands, run in the subcutaneous cellular tissue towards the root of the limb. \* \* \* They diminish in number as they are traced upward. In the forearm there are about thirty, but in the middle of the arm only about fifteen to eighteen. In the forearm they tend to divide themselves into groups, an external, \* \* \* an internal, \* \* \* and a middle group. The majority of these collectors run as far as the neighborhood of the base of the axilla. Here they penetrate the deep fascia, and terminate in the humeral

chain of axillary glands. Two or three of the most internal (collectors) end in the epitrochlear gland. \* \* \* The epitrochlear gland is not constant: but is usually to be found. Of small volume and slightly flattened it rests on the humeral aponeurosis and thus is covered not only by the skin, but by the entire thickness of the underlying fatty cellular layer; hence the difficulty and often the impossibility which one experiences in its palpation. Sometimes there are two and more rarely three situated one above the other in series and connected by efferent vessels. The pathologists consider the enlargement of this gland as indicating lesions of the trunks which form the posterointernal group and more particularly of those which originate in the two inner fingers. Often, indeed, this opinion is justified by observation but it must not be forgotten that this swelling may also occur with lesions related to the radial side of the hand or of the forearm: it is then explained by the very rapid generalization of the inflammation, a generalization which the numerous anastomoses established between all the lymphatic trunks of the upper limb facilitate."

Poirier and Charpy<sup>9</sup> say, "The epitrochlear gland is ordinarily placed three or four centimeters above the epitrochlea. \* \* \* When this gland is not enlarged it is difficult to find it by palpation."

Leaf<sup>10</sup> says: "The antecubital glands are variable in number; frequently none are present. Most usually a small gland is found one and a half inches above and slightly to the outer side of the internal condyle; this is, of all the antecubital glands, the most constant. Often a gland is found below this three fourths to one inch above the internal condyle. Both these glands are usually superficial to the deep fascia but occasionally lie underneath it."

Delamere<sup>11</sup> says: "According to Stahr the lymphatic vessels of a given region pass through three distinct glandular stages during their course. First of all, there are the small nodules of interrupted glands (Schaltldrüsen) whose presence is inconstant, and number variable, \* \* \* then come the regional glands (Regionendrüsen), where the glands are larger and more constant. Finally, there are the intermediary glands, (Intermediardrüsen).

"There are transitional forms between the Schaltldrüsen and the regional glands; such are the epitrochlear and the anterior tibial glands."



From this description of the anatomy of the epitrochlear gland it will be seen (1) that it drains a definite and quite restricted area; (2) that it is the first gland through which the lymph stream from the extremity passes; (3) that it is not covered by any layer of fascia; (4) that it rests upon a firm bed of aponeurosis, and (5) that there are no neighboring or overlying structures to interfere with its palpation except the panniculus adiposus and the skin.

#### REVIEW OF THE LITERATURE

Virchow<sup>12</sup> in 1860 suggested that, as in cancer, the glands serve as depots for the virulent material, thus for a time protecting the rest of the system from its influence, and finally, after complete impregnation, and under favoring conditions, occasionally acting as new foci of infection for the general economy.

Sigmund<sup>13</sup> quoted by Bumstead and Taylor<sup>18</sup> and by de Amicis<sup>19</sup> seems to have been the first to insist on the importance of epitrochlear enlargement as a diagnostic sign of syphilis.

Campana<sup>14</sup> in 1870 called attention to the superficial adenopathies in an article in which he discussed their pathologic changes, and gave considerable attention to the superficial glandular enlargement occurring in congenital syphilis. He stated that the differentiation between syphilitic and tuberculous adenitis was important and thought that the most commonly enlarged glands in secondary syphilis were (1) lateral and posterior cervical; (2) the submaxillary; (3) the axillary; and (4) the inguinal and (5) less often, the epitrochlears.

Madier,<sup>15</sup> the translator and reviewer of Campana's work, does not agree with that author as to the frequency of superficial adenitis in congenital syphilis, and calls attention to the fact in a protesting footnote.

Otis,<sup>16</sup> in 1871, read an extraordinary paper before the Medical Society of the County of New York in which he advanced the theory that the incubation period of syphilis is that period of time required for the syphilitic disease germ to traverse the distance from the point of inoculation to the interior of a lymphatic. He concludes that a satisfactory explanation of some of the later manifestations of syphilis may be found through causes wholly dependent upon interference with the lymphatic circulation and that it is through

the lymphatic system alone that the syphilitic influence is propagated to points remote from the site of inoculation.

Fournier,<sup>17</sup> lecturing to his students in 1872, on the secondary adenopathies of syphilis divided the glands into four groups in the order of their frequency of involvement. These groups were (1) posterior cervical, occipital, and mastoid; (2) anterior cervical, in which he includes the "peripharyngeal," the "subhyoid," and the "inferior cervical"; (3) the submaxillary; and (4) the inguinal, the parotid, the pre-auricular and the epitrochlear. Not content with putting the epitrochlear gland in last place, he adds a footnote which follows: "In regard to this last adenopathy I ought to say that its frequency has been greatly exaggerated, in referring to it as an habitual or common sign of syphilis. I have searched for it with scrupulous care in many hundreds of patients both men and women and have never encountered it except on rare, almost exceptional occasions." In the same lecture he says, "It is during the secondary period, at its onset or during its first months, that the adenopathies most commonly appear. It is not rare to observe them a little later, in the course of the second year, for example. But further on they become less and less common, and after about the third year they are scarcely ever found. To take an extreme example, they are never found after ten, fifteen, or twenty years of infection. At this stage, if they once existed, they have long since ceased to be palpable, and to search for them, after such a long period shows more than superfluous care. Therefore, gentlemen, do not imitate these incompetent clinicians who, confronted with the problem of diagnosing either a recent chancre or a late tertiary lesion, set about examining with scrupulous care the cervical region of their patients. For that is to prove one's ignorance, it is the commission of a pathologic anachronism, when one endeavors to find secondary adenopathies at a period of the diathesis to which they do not belong."

In Fournier's treatise on syphilis published in 1899,<sup>7</sup> he modified his opinion in regard to the groups of glands most frequently involved, stating that the predilection of secondary syphilis for certain glands which it affects by preference over all others is a curious phenomenon. These glands he says, are (1) the posterior-cervical, (2) the anterior-cervical, and (3) the epitrochlear. With regard to

the epitrochlear gland he said: "Less frequent, but much more curious, by reason of its singular locality and of the absence of any satisfactory explanation for it, is the enlargement of the epitrochlear gland. It is subject to several variations. Thus, it may be unilateral or bilateral. It may consist of one gland or, more rarely of two or three." Fournier still insists, however, that this adenopathy gradually resolves without new phenomena and that the glands finally atrophy and disappear. However, he calls attention to the article of de Amicis who claims that the adenopathy persists over a long period of years, and says that these observations deserve to be checked up by further observation.

Augagneur,<sup>18</sup> in 1895, stated that the primary and secondary adenopathies are not so much a sign of the intensity of the infection as one of the vigor with which the individual resists the infection. His argument was that acquired syphilis in children causes enormous and persistent glandular enlargement, and that in this class of cases the disease is very benign. On the other hand, in the aged, where the glands have atrophied, the disease is very severe. Finally, that in the fetus there is direct inoculation without the intervention of phagocytosis and that in congenital syphilis the disease is of extreme gravity. He thought that when the adenopathy was intense the syphilis was mild and was a favorable prognostic sign. He concluded that there is reason for favoring phagocytic activity by the use of certain lymphatic stimulants such as salicylic acid.

De Amicis<sup>19</sup> in 1896 published the article to which Fournier refers. He disagreed with Augagneur's opinion that the greater the adenopathy the milder the disease and the more favorable the prognosis. In support of this he reports in detail fourteen cases of grave syphilis with marked glandular reactions. He says, "The presence of enlargement of the epitrochlear gland if not constant as Sigmund has claimed is certainly not rare as has been stated by Thiecmeyn; one would not be far wrong in saying that epitrochlear adenopathy is the pulse of syphilis." He reviewed the records of the outpatient clinic in dermatology and syphilis (Naples) for 1895-1896 and found that in 2119 cases of syphilis epitrochlear enlargement was recorded in 481. On the other hand, he said, Professor T. de Amicis in his private clinic failed to find this sign present in only 13 out of 100 cases and that in 10 cases of late syphilis



epitrochlear enlargement was absent in only three. The difference in percentage of positive findings between the public and the private clinics he explained by saying that the examination of the glands is often omitted in the public clinic.

De Amicis reported a case first seen with a healing chancre 70 days after exposure. There were no skin or mucous membrane lesions; the inguinal and cervical glands were barely palpable, but both epitrochlears were markedly enlarged. The patient was advised to return in three weeks and at the second examination presented a macular roseola. At this time the epitrochlears were still more enlarged and there was some infiltration of the right inguinal gland, none on the left, and no palpable cervical glands. He considered specific epitrochlear enlargement very obstinate and said that although it may disappear at the same time as the adenopathy in other regions, it often persisted, and by its permanence became the only sign directing the clinician to the recognition of the latent form of syphilis of many years' duration.

De Amicis reviewed the literature in regard to gumma of the lymphatic glands and concluded that it might appear as early as the fourth year after infection and that it might be either unilateral or bilateral. He reported eight cases of gumma of this gland seen at the Naples clinic during the years 1905-1906 and gave autopsy report with histologic and bacteriologic findings.

His conclusions were that epitrochlear adenopathy is one of the most frequent syphilitic manifestations; that its absence might very well depend on anomalous physiologic deficiency of the gland; that its enlargement is not dependent on infection injuries in the drainage area but was an evidence of general infection; that it might accompany the enlargement of other superficial glands or occur alone; that it accompanied the tertiary period as well as the secondary and might be found, though less commonly, in the primary stage; that it might persist when the adenopathy in other regions had subsided and for this reason had great diagnostic value; finally, he said that epitrochlear adenopathy, while not an unequivocal sign of constitutional syphilis, since present in the course of several other of the general infections, was certainly one of the most important facts in the symptomatology of this infection, and its presence—when enlargement from infective conditions in the drainage area

could be excluded—was a valuable sign in cases of doubtful diagnosis and permitted the recognition of latent syphilis, especially when not associated with glandular enlargement in other regions.

Musser,<sup>20</sup> in 1904, said that enlargement of the postcervical and epitrochlear glands, and lymphatic glands in other portions of the body points to syphilis. In the first two mentioned localities the enlargement is of great diagnostic importance, as it is less likely to be due to any other cause.

Montgomery and Culver,<sup>21</sup> in 1910, discussing the diagnosis of luetic lymphoma in late syphilis said that after excluding recent syphilis and the acute fevers one must consider the possibility of ten causative diseases; actinomycosis, blastomycosis, granuloma coccidioides, leucemia, endothelioma, pyogenic infection, carcinoma, tuberculosis, lymphosarcoma (Hodgkin's disease), and late syphilis. They gave the differential points leading to a diagnosis.

Horbsinger<sup>22</sup> and Heubner<sup>23</sup> regarded epitrochlear enlargement in children as nearly always syphilitic.

Finkelstein<sup>24</sup> agreed with this conclusion but modified his view by adding that epitrochlear enlargement with other evidence of syphilis is significant. Horbsinger said that epitrochlears are always palpable in syphilitic nurslings.

Reiche<sup>25</sup> in 1908 reported that of 235 children examined 13 had known syphilis and nine of these had palpable adenopathy of the epitrochlears. His conclusions are that epitrochlear adenopathy is not exclusively syphilitic; that its diagnostic significance is to be regarded with circumspection and is of value only with other specific manifestations, and that it is not pathognomonic of syphilis.

Grosser and Dessauer<sup>26</sup> in 1911, and Goldreich<sup>27</sup> in 1912 published statistics of epitrochlear adenopathy in children and its occurrence in syphilis and other conditions, especially rachitis and tuberculosis. If their figures are combined, it is possible to show findings in nearly three thousand cases. Of 2737 nonsyphilitic children 312 had palpable epitrochlears on one or both sides, a percentage of positive findings of 11.2. Of the 312 positive cases 78, or about 25 per cent were either rachitic or tubercular. In a total of 241 syphilitic children (combined figures) epitrochlear adenopathy was present in 192, or 79.67 per cent; 19.93 per cent of these adenopathies were unilateral.

Goldreich concluded that the stigmata of latent congenital syphilis are often so characteristic that a competent clinician can diagnose the condition with certainty even in the presence of a negative Wassermann; that epitrochlear adenopathy with other stigmata of syphilis offers a valuable aid in diagnosis both in nurslings and in children generally during the first five or six years. He stated that the Wassermann reaction is an invaluable aid in the diagnosis of latent congenital syphilis but was found negative in one third of the cases reported by him.

Coerper,<sup>28</sup> in 1916, reported his findings in a large number of examinations of the superficial glands in children. He found that 1000 children two years of age all showed more or less glandular enlargement. In 1000 cases of various ages from which latent syphilis was not thoroughly excluded he found the epitrochlears enlarged on one or both sides in 120. He concludes that syphilis and sepsis cause multiple adenopathies; tuberculosis causes enlargement of only a few glands; one cubital or pectoral gland is not specific for syphilis but in chains they are very suspicious; chronic nutritional disturbances cause enlargement of most of the superficial glands; and children fed on breast milk have fewer adenopathies than artificially fed children.

Batut,<sup>29</sup> in 1909, stated that epitrochlear adenopathy was a reason for suspecting syphilis but adds that he has noticed this sign often in tuberculous subjects, so that it is not absolutely characteristic. He thought that, in the absence of otorrhea and bone tuberculosis, pediculosis capitis and eczema of the scalp, adenitis of the occipital and mastoid glands warrants a positive diagnosis of syphilis.

In 1912 Friedlander<sup>30</sup> collected statistics of the condition of the superficial glands in one hundred definitely syphilitic cases with positive Wassermans and one hundred definitely nonsyphilitic cases with negative Wassermans. Obese patients were excluded from both groups. He gave some very instructive tables and from his analysis concluded that (1) there is a universal adenopathy in syphilis; (2) that the enlargement of certain syphilitic glands is more characteristic than others and they rank in the following order: a. epitrochlear, b. occipital, c. postcervical; (3) the proportion of enlarged glands decreases in direct ratio with the age of the



infection and (4) the bilateral glandular enlargements are of more significance than the unilateral.

In Power and Murphy's work<sup>31</sup> published in 1914 Andrews (i, p. 129) gives the superficial glands in the order of importance that he considers they deserve as follows: (1) anterior cervical, (2) posterior cervical, (3) suboccipital, and (4) epitrochlear. In the same volume Lambkin, (p. 204) gives adenopathy first place among the secondary symptoms and arranges the glands in the following order: (1) posteervical, (2) occipital, (3) submental, (4) axillary, and (5) mastoid.

Shillitoe<sup>31</sup> in the same work, speaks of a universal enlargement of the superficial lymph glands, and probably the deep also, as being occasionally the first effect of the general invasion of the system in women. He says, "I lately saw a case in whom, previous to the outbreak of any secondary eruption, almost every superficial gland in the body could not only be felt but could be plainly seen \* \* \* This general enlargement of the lymph glands was at the time the only confirmatory evidence present as to the nature of the chancre, the whole forming as perfect an illustration of the superficial lymph glands of the body as one could wish to see."

McDonagh<sup>32</sup> in 1916 made the following statement: "Those cases in which the lymphatic glands are most enlarged are usually those in which the infection is slight, and histologic examination reveals the smallest number of parasites. Those cases in which the lymphatic glands are smallest and hardest, are usually those in which the infection is severe, and a histologic examination reveals the largest number of parasites. Therefore a ratio exists between the size of the glands and the protective capacity of the host against the disease."

Keyes<sup>33</sup> in his book on syphilis published in 1908 said (p. 118): "General syphilitic adenitis usually follows closely upon the first general eruption, and disappears well within the year. Hence *syphilitic adenitis is extremely rare after the first year.*" And on page 263 of the same work: "The secondary adenitis lasts usually from one to three months, very rarely into the second or third year. Hence it is absurd to depend upon it for a diagnostic aid after the first few months of the disease. To 'diagnose syphilis from the

state of the nodes' is a perilous venture." This is reminiscent of Fournier's lecture in 1872.

Montgomery,<sup>6</sup> in 1917, contrasted strikingly the unfavorable conditions found in the blood vascular system and the favorable ones occurring in the lymphatic system for the growth of spirochetes.

Pottenger,<sup>34</sup> in 1917, said: "Infection of many body structures at one time rarely occurs in tuberculosis, except as one of the manifestations of the later stages of the disease, while it is the rule in syphilis from the time of the first escape of the treponemata from the lymphatic glands."

Warthin,<sup>35</sup> 1918, said, "The lymph nodes of the older cases of syphilis (even in young individuals) were atrophic and presented lymphoid atrophy, chronic sinus catarrh and hyaline formations (scars) in the germ centers and lymphoid tissue. In younger cases the nodes are frequently hyperplastic, but the germ centers, while enlarged, show a marked leucocyte exhaustion. Their appearance indicates a continuous demand made upon these organs against a persistent infection."

Sutton<sup>36</sup> said: "Too much diagnostic value should not be placed on the presence of palpable lymph nodes, however, especially in thin persons and in individuals who are subjects of lymphatism. In obese persons, on the other hand, great difficulty may be experienced in locating the involved structures, even though they may be both swollen and indurated."

Hazen,<sup>37</sup> in his book on syphilis, 1919, discussed the lymphatic reaction in syphilis and quoted Friedlander's work. He spoke of enlargement of the "submammary" (pectoral) lymphatic glands as being of diagnostic value.

Doumer,<sup>38</sup> in a 1920 Paris thesis, said that epitrochlear adenopathy was more common in mild cases than in severe ones. He found that the presence of this sign in nonsyphilitic cases was very exceptional if cases of local infection, leucemia, and mycosis fungoides were excluded. In discussing tuberculous adenitis he said that Levy-Frankel has examined all cases of tuberculosis coming under his observation at St. Louis Hospital over a considerable period and has failed to find epitrochlear adenopathy in any case, even in children with tubercular adenitis in other regions. He gave the "domain of scrofula" as: the anterior cervicals, the submaxillaries,

the inguinals, and the external iliac glands. "When added to these one finds adenopathy of the postcervicals, the mastoid and especially of the epitrochlear glands it is necessary to consider the subject syphilitic."

He thought that, "One is warranted in concluding that aside from syphilis there is no disease which causes epitrochlear adenopathy and conversely in every case showing this sign one can be sure that syphilis exists."

Brown and Pearce,<sup>1</sup> 1920, said, "\* \* \* the assumption seems warranted, therefore, that while the spirochetes are widely distributed over the body during latent as well as active periods of infection, the distribution is not an indiscriminate one but that the chief reservoirs of infection are the lymphoid structures of the body whether massed as in the case of the lymph nodes or in the form of the simpler perivascular lymphatics. This points to the possibility of a wider application of our knowledge of lymphoid involvement in diagnostic and prognostic measures."

#### METHOD OF PALPATION

In the palpation of the epitrochlear gland the elbow of the patient is flexed nearly to a right angle, and the forearm is supported by the hand of the examiner corresponding to the side being examined so that the arm muscles are relaxed. The other hand of the examiner is placed above the internal condyle with the four fingers exerting pressure outward and backward on the arm. In this position the examining hand is moved up and down, putting an even pressure on the fascia through the skin and subcutaneous tissue. If palpable the gland will usually be felt as a pea-sized, movable, hard, elastic mass. Some examiners move the fingers transversely across the deep fascia in searching for the gland, but movement of the hand in the long axis of the arm is a surer method and less confusing because the deep fascia in some patients is ribbed longitudinally and may give the impression of a separate mass which does not really exist. The entire width of the fascia should be palpated since the gland is quite variable in location.

The only other structures lying on this fascia are the basilic vein and the internal cutaneous nerve. As the lymphatic vessels accompany the vein and the latter pierces the fascia near the middle of



the arm it is not useful to palpate for the gland higher than the midarm. However, the gland is often palpable at a distance above the internal condyle greater than is indicated in the foregoing summary.

Anatomists agree that the epitrochlear gland is inconstant. Unfortunately they do not state the percentage of cases in which it is absent, misplaced, unilateral or multiple. In the absence of definite figures perhaps it is justifiable to take those collected from cases of secondary syphilis in this series and to say that the gland is probably absent, rudimentary or misplaced on both sides in from 10 per cent to 14 per cent of individuals; that it is unilateral in from 14 per cent to 20 per cent and that it is bilaterally present and sufficiently developed to be palpable when enlarged in 72 per cent to 75 per cent of individuals. In probably 3 per cent of individuals the glands on one or both sides are multiple, usually two, but as many as five having been palpated.

The frequently expressed opinion that unilateral epitrochlear enlargement is of less diagnostic significance than bilateral does not seem to be well founded. In all probability it is partly due to the assumption that unilateral adenopathy of this gland is relatively common as a result of infections of the hand and forearm. If this assumption had a solid basis of fact one would expect to find unilateral adenopathy much more common on the right side, since this arm is more used and more exposed to injury. The cases in this series do not support this theory. Dividing these cases relative to the stage of the disease the distribution is shown in Table I.

TABLE I

UNILATERAL ADENOPATHY	RIGHT	LEFT
Primary syphilis	3	6
Secondary syphilis	6	9
Tertiary syphilis	16	10
Total	25	25

The only conclusion that seems justified by these figures is that on one side or the other, the gland is congenitally absent, rudimentary or anomalously located in from 15 per cent to 20 per cent of individuals. No other explanation of the fairly constant percentage of unilateral findings in all stages and types of the disease seems

adequate to explain its occurrence in a condition produced by a general infection.

The statement recurs persistently in the literature that epitrochlear adenopathy and adenopathy in general is less constantly found and is less marked in cases presenting severe secondary symptoms than in those of a milder type. Augagneur<sup>18</sup> devoted a paper to the support of this proposition and recently Doumer<sup>38</sup> has reasserted its truth in one of the Paris theses for 1920. On the other hand De Amicis disputed this statement and recorded a series of severe cases in which epitrochlear enlargement was also present.

Analysis of the secondary chart of this series does not give data warranting the continued acceptance of this statement. Of 88 cases in which the symptoms are recorded with enough detail to warrant classification Table II shows the analysis.

TABLE II

SECONDARY SYMPTOMS	NUMBER OF CASES	EPITROCHLEARS NOT PALPABLE	PERCENTAGE OF POS. FINDINGS
<i>Denied</i>	21	1	95.3 %
<i>Mild</i>	30	3	90.0 %
<i>Severe</i>	37	3	91.9 %
Combining the mild cases with those in which all secondary lesions are denied, the figures become:	51	4	92.1 %

From the above it seems evident that if there is a variation in the frequency of epitrochlear adenopathy in inverse relation to the severity of mucocutaneous symptoms it must be very slight indeed.

The work of Brown and Pearce in experimental syphilis in rabbits has led them to think that the amount of antibody formation is closely associated with the amount of tissue reaction; for example, the larger the chancre and the longer its duration, the less severe the following secondary manifestations.

If the conclusions drawn from their series of experiments on this problem are applicable to human syphilis, they should help to justify the persistence of the clinical observation referred to above, and to render intelligible the decreased frequency of adenopathy in neurosyphilis as compared with other forms of the disease, which will be referred to later.

*Nonsyphilitic Conditions In Which Epitrochlear Adenopathy Occurs:*

Actinomycosis.  
Blastomycosis.  
Granuloma coccidioides.  
Mycosis fungoides.  
Leprosy.  
Endothelioma.  
Carcinoma.  
Lymphatism.

Acute eruptive fevers, including glandular fever.  
The leucemias.  
Lymphosarcoma (Hodgkin's disease).  
Rachitis.  
Tuberculosis.  
Infections of the hand and forearm.  
Chronic generalized pruritus from any cause.

The diseases in the first group are so uncommon that no further mention will be made of them. Their differentiation from syphilis is not ordinarily difficult. Lymphatism is not common and occurs in children. The deeper lymphoid tissues, thymus, etc., are involved to a much greater extent than the superficial. The accompanying anemia and dyspnea aid in diagnosis.

The adenopathy accompanying the eruptive fevers is well known. It disappears after the acute attack has subsided, usually within a few weeks, in uncomplicated cases.

The leucemias and Hodgkin's disease are less easily differentiated but examination of the spleen and the cervical region together with the history and the blood picture usually suffice to put the clinician on his guard.

Rachitis and chronic nutritional disturbances in children lead to adenopathies. From the statistics of Grosser and Dessauer<sup>26</sup> and Goldreich<sup>27</sup> it appears that about 27 per cent of children with rachitis have epitrochlear enlargement. However, this condition of the glands is due to faulty metabolic equilibrium, and if the balance is restored, the glands again become normal.

Tuberculosis in children, according to the same authors, gives an enlargement of this gland in about 20 per cent of cases (combined data).

On the other hand Levy-Frankel<sup>30</sup> declared that it never occurred even in children with scrofulous glands in other parts of the body.

McKee and Wells,<sup>40</sup> speaking of children, said that 70 or 80 per cent of enlarged cervical glands are tuberculous; and that in tuberculous adenitis usually the entire lymphatic system is more or less



affected. Polyadenitis in children, they think, may be considered a diagnostic sign of tuberculosis.

Edmunds,<sup>41</sup> speaking of the supracondylar gland, says, "It is rare to find these glands affected in tuberculosis, but the condition is occasionally met with in connection with tuberculosis of the bones of the hands." Apparently one may conclude that tuberculosis must be thought of in epitrochlear adenopathy in children but that it is uncommon in adults.

Infections of the hand and forearm can usually be excluded from the history and physical examination, furthermore they are usually unilateral and in recent cases the gland is tender. If the infection has been severe enough to cause permanent enlargement of the epitrochlear gland evidence of other damage will usually be found in the form of scars.

Chronic generalized pruritus is a frequent cause of general adenopathy and is not often mentioned in this relation. Most cases of old scabies, pediculosis corporis, chronic generalized eczema, dermatitis herpetiformis, etc., will be found to have palpable epitrochlear glands, and all cases of this type have been excluded from this series.

The cases comprising this series have been selected from among 3200 cases admitted to the syphilis clinic at Bellevue Hospital, New York, during the past year.

I wish to express my thanks to Dr. M. B. Parounagian, director of this department, for permission to use the material and for his interest and assistance in the work.

In selecting cases only males were included; there were two reasons for this, one, the greater amount of subcutaneous fat usually present in female patients, the other, the fact that in women the chancre often goes unnoticed, the incubation period is seldom ascertainable, and in general the disease runs a less typical course than in men.

Fat patients were excluded because of the difficulty in doing accurate palpation. Patients with evident lesions or having diseases other than syphilis, that commonly produce general adenopathy, were excluded in order to make the findings relative to syphilis

In the nonsyphilitic cases painstaking efforts were made in obtaining more accurate.

taining the history, laboratory tests, and necessary physical examinations. In cases where these had not been attained, the record was excluded from the chart. This explains the small number of cases found in the nonsyphilitic group.

In a large clinic many cases are transient and their records are never completed. Nevertheless it is somewhat humiliating to find that, among over three thousand cases, records covering the desired details were available in only about one tenth. Although this seems to be the prevailing condition in most clinics, I cannot escape chagrin since I am responsible for the examination of the new cases.

In classifying cases as primary, secondary or tertiary it was necessary to be somewhat arbitrary since the use of these terms is open to severe criticism from a purely scientific standpoint, and different authorities have different views as to the clinical boundaries applicable to their use. In the primary group were included cases without evident secondary lesions, adenopathy excluded, in which the elapsed time since the appearance of the chancre was not more than three months. In the secondary class were included cases with frank secondary lesions and cases in which the infection had been present more than three months and not more than two years. In the tertiary group were included all cases in which the duration of the disease was over two years.

While this division of the cases is open to grave objections, it was adopted because of its convenience and because it was thought to represent the average concept created by the use of these terms.

Scores of cases were excluded in which the diagnosis was questionable or the history or record of physical examination contained evident errors. It is believed that the cases tabulated (Table III) represent the conditions under which they are classified with as great accuracy as is possible under working conditions at the clinic.

#### ANALYSIS OF 42 CASES OF PRIMARY SYPHILIS

The diagnosis of 14 cases was based on positive dark-field findings. Of these 14 cases epitrochlear adenopathy was present in 8 and not appreciable in 6.

Five cases were diagnosed in which both the dark-field examination and the Wassermann test were positive. Epitrochlear enlargement was observed in 2 of these cases and not found in 3.

TABLE III

SUMMARY OF 252 CASES OF SYPHILIS AND 43 NONSYPHILITIC CASES IN RELATION TO EPITROCHLEAR ADENOPATHY				
<i>Syphilitic Cases—All Stages—252 Cases</i>				
Percentage of negative findings				21.
“ “ positive “		(bilateral)		59.16
“ “ “ “		(unilateral)		19.84
“ “ “ “		(combined)		79.
<i>Primary Syphilis—42 Cases</i>				
Percentage of negative findings				33.33
“ “ positive “		(bilateral)		45.24
“ “ “ “		(unilateral)		21.43
“ “ “ “		(combined)		66.67
<i>Secondary Syphilis—94 Cases</i>				
Percentage of negative findings				12.77
“ “ positive “		(bilateral)		72.34
“ “ “ “		(unilateral)		14.89
“ “ “ “		(combined)		87.23
<i>Tertiary Syphilis—116 Cases</i>				
Percentage of negative findings				23.27
“ “ positive “		(bilateral)		56.9
“ “ “ “		(unilateral)		19.83
“ “ “ “		(combined)		76.73
<i>Nonsyphilitic Cases—43 Cases</i>				
Percentage of negative findings				76.75
“ “ positive “		(combined)		23.25

NOTE: When the chart of nonsyphilitic cases was begun the unilateral and bilateral cases were not separated. Later this was done, but it was not possible to re-examine certain cases. The figures on this point are therefore inaccurate, and are not included.

Fifteen cases were Wassermann positive and dark-field negative and of these epitrochlear adenopathy was present 11 times and absent 4 times.

Eight cases were diagnosed clinically, both dark-field examinations and Wassermann reactions remaining negative. Of these cases 7 showed epitrochlear adenopathy and one was negative.

In 27 cases dark-field examinations were made and of these 19 eventually gave positive findings: percentage positive—70.4. However the first dark-field was negative in 14 of the 27 cases: percentage positive findings (first examination)—44.44. In the same series of 27 cases epitrochlear adenopathy was found on admission in 15 cases: percentage of positive epitrochlear findings—55.55. Of the 41 cases in which the Wassermann test was done a report of one-plus or stronger was obtained in 20 cases: percentage positive—48.8. However, the first Wassermann test was anticomplementary,



negative or plus-minus in 25 of these cases: percentage of positive reactions (first examination) 39.1. In the same series of 41 cases epitrochlear adenopathy was detected on admission in 27 cases: percentage positive findings—65.85.

The incubation period is given in 19 cases. It varies from 10 to 68 days, with an average of 28.7 days. In these 19 cases the chancre had appeared from 2 to 95 days before admission, with an average elapsed time of 25 days: the average time between infection and admission was 53.7 days. Of these 19 cases 15 had palpable epitrochlears, (79 per cent), and 4, (21 per cent) did not.

The average period since infection in the fifteen positive cases was 55.73 days. The average period since infection in the 4 negative cases was 46 days. (If one of these cases is eliminated the figures become 36.)

In 40 cases the elapsed time between the appearance of the chancre and examination was given. The average was 30 days. Analysis of these cases is shown in Table IV.

TABLE IV

TIME ELAPSED SINCE APPEARANCE OF CHANCRE	NUMBER OF CASES	POSITIVE EPITROCHLEARS	PERCENTAGE OF POSITIVE
1 to 14 days	16	8	50.
15 to 30 days	13	10	76.9
Over one month	11	8	72.7

These figures include as positive the combined unilateral and bilateral examinations. The number of cases in the individual groups is so small that the percentages would probably be more constant in a larger series, but the analysis is thought interesting as showing that the adenopathy undoubtedly appears early in a percentage of cases, and that the positive findings probably become more frequent as the secondary stage is approached.

Although the study of these cases is carried rather far, it is thought justifiable as showing that appreciable epitrochlear adenopathy occurs in the so-called primary stage of syphilis in a fairly large percentage of cases, that this percentage increases as the classical secondary stage approaches, that the frequency of epitrochlear adenopathy in primary syphilis compares favorably with the percentage of positive dark-field and Wassermann reactions, and

finally, that it is the first clinical evidence of generalized syphilis in two-thirds of these cases.

#### SECONDARY SYPHILIS: 94 CASES

Epitrochlear adenopathy was not detected in 12 of these cases (12.77 per cent). It was present bilaterally in 68 cases (72.34 per cent), and unilaterally in 14 cases (14.89 per cent). Combining the unilateral with the bilateral figures there are 82 positive cases (87.23 per cent).

In 92 cases the Wassermann test was tried one or more times. The *first* Wassermann was one-plus or stronger in 72 cases (78.26 per cent) and negative, anticomplementary or plus-minus in 20 cases (21.74 per cent).

Later tests improved these figures so that the reaction was recorded as positive in 76 cases (82.6 per cent).

One or both epitrochlear glands were palpable in 80 of these 92 cases (87 per cent). In the 12 negative cases the Wassermann test was present as follows: four-plus—six times; three-plus—four times; one-plus—twice.

#### TERTIARY SYPHILIS

(Analysis of Chart of 116 Cases)

##### *Epitrochlear Adenopathy*

Not present in 27 cases:	Percentage of negative findings—23.27
Present bilaterally in 63 cases:	Percentage of positive findings—54.31
Present unilaterally in 26 “ :	Percentage of positive findings—22.42
Combining unilateral and bilateral cases:	Percentage of positive findings—76.73

In 15 of the 116 cases the duration of the infection is uncertain or not given. In the remaining 101 cases the average duration was 10 years.

In analyzing these 101 cases they were divided into five-year groups in an effort to determine the persistence of the adenopathy.

TABLE V  
DURATION OF THE DISEASE

DURATION	NUMBER OF CASES	EPITROCHLEARS PALPABLE
5 years, or less	33	29 or 88 %
6 to 10 years	28	22 or 78.5 %
11 to 15 “	16	10 or 62.5 %
16 to 20 “	13	9 or 69.2 %
Over 20 “	11	10 or 90.1 %

This analysis seems to show that the adenopathy is very persistent or permanent and the variations in percentage in the different groups is probably due to the fact that not enough cases are tabulated for constant findings.

An interesting point arises when an analysis of the cases with negative epitrochlear findings is attempted. Of the 116 cases charted, 27 did not show epitrochlear adenopathy. Of these 27 cases 11 (40.74 per cent) showed signs of neurosyphilis. Because of this observation cases of neurosyphilis were extracted from the tertiary group and examined with the following results.

Of a total of 23 cases giving signs of syphilitic involvement of the central nervous system 11, or 48 per cent, did not show epitrochlear enlargement. Nine, or 39 per cent, were positive bilaterally and 3, or 13 per cent, were positive unilaterally. Combining the unilateral and bilateral adenopathies the percentage of positive findings becomes 52.

Since these percentages are strikingly low, much lower than even in primary syphilis, all these cases were temporarily excluded. This left 93 cases to be considered and in these the percentage of negative epitrochlear examinations was found to be only 17.2 (16 cases), while the percentage of palpable glands (bilateral and unilateral combined) was found to be 82.8.

While the number of cases of neurosyphilis considered is not large enough to warrant positive statements, it seems probable that cases that eventually develop nerve syphilis either do not show the usual reaction of the lymphatic system to the infection or, that the adenopathy, which seems to be so persistent in other forms of the disease, is transient in cases destined to show involvement of the central nervous system.

#### WASSERMANN REACTION

The Wassermann test on admission in the 116 cases under consideration was negative, anticomplementary or plus-minus in 32 cases, or 28.2 per cent. It was one-plus or stronger in 84 cases, or 71.8 per cent. Five cases, negative on the first examination gave positive reactions after repeated examinations so that the final showing of the Wassermann test in this series becomes: Positive—76.73 per cent. Negative—23.27 per cent.



Of the 32 cases in which the Wassermann test was not positive on admission 26 had palpable epitrochlear glands on one or both sides.

Of the five cases which later gave Wassermann reactions four had palpable epitrochlear glands.

Of the 27 cases in which the Wassermann test was persistently negative 22 had palpable epitrochlears on one or both sides.

Fifty-two cases in this series had had treatment at some time before coming to the clinic. Of these cases 32 gave positive Wassermann reactions and 20 negative. The epitrochlear findings were positive in 42 of these cases, or 81.9 per cent.

#### CONCLUSIONS

1. Epitrochlear adenopathy is an early, persistent, and common sign of syphilitic infection.

2. It is not pathognomonic, for the condition occurs in nonsyphilitic individuals.

3. It is a valuable aid in diagnosis during a period of the primary stage when both the dark-field examination and the Wassermann test are often negative.

4. It is valuable in treated and latent cases, and when present calls for repeated laboratory tests before the possibility of syphilis can be excluded.

5. Since the condition is unilateral in one-fifth of the cases of syphilis, the statement that unilateral adenopathy is nonspecific is not warranted and cases presenting this condition should be investigated with the same care as when bilateral adenopathy exists.

6. Treatment does not cause complete resolution of specific epitrochlear adenopathy.

7. Epitrochlear adenopathy is less common in neurosyphilis than in other forms of the disease.

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## SILVER ARSPHENAMINE

By W. H. GUY, M.D., AND FRED M. JACOB, M.D.

PITTSBURGH, PA.

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SILVER arsphenamine, first mentioned by Ehrlich and completed by Kolle in 1918, has been given a thorough trial in many clinics in Germany and several other continental countries. The literature from these sources is voluminous and gives in general a very favorable report on the drug. The use in this country is still limited and the few American reports are somewhat varied.

The drug is arsphenamine chemically combined and alleged to be biologically reinforced with silver. The content is arsenic 22 per cent and silver 14 per cent. Reports from the U. S. Public Health Service indicate that the trypanocidal activity is about three times that of arsphenamine so that .2 gm. of silver arsphenamine shows the same effect on lesions as .6 gm. arsphenamine. The toxicity of silver arsphenamine as reported from animal experiments is at least no greater than that of arsphenamine, but reports as to the toxicity in humans varies so that the size of the dose is as yet not fully determined. Thus the determination of dosage and the immediate effect on the patients is still to be found and the ultimate result of its use is a matter for future observation.

Silver arsphenamine is a dark brown powder which, in sealed vacuum ampoules, will keep indefinitely, but rapidly decomposes and becomes very toxic when exposed to the air. It is easily soluble in cold water, forming a dark brown solution very much like colloidal silver preparation. Decomposed solutions are opalescent, and highly toxic. It has been administered in two ways, viz.: in dilute solution by the gravity method and in concentrated solution by syringe. Both are claimed to be less toxic by their various adherents. Both were tried in our clinics.

The technic of the first method is as follows: The drug is dissolved in a few c.c. of cold distilled water and the bulk of the solution is made up with .4 per cent saline solution. The dilution

recommended by the makers and most frequently used is .1 gm. to 30 c.c. of solution. This solution is given by the gravity method in .25 gm. to .3 gm. doses in adults. The usual technic as to the sterility and filtration holds, but cold water is always used and solutions are given very soon after preparation on account of the rapid decomposition. Indications, contraindications, and intervals of dosage, etc., are the same as for arsphenamine.

Walson, Kerl, Ahman and a few others use the concentrated solutions. Their technics differ slightly as to details, but in general are the same as the following used by us after trying the above. The drug is dissolved in cold, distilled water in a small glass container by sprinkling the powder on the surface of the water. It dissolves readily in about one minute with no other manipulation than lightly tapping the side of the glass. A 2 per cent solution is made and the required dose drawn into a large glass syringe after filtration. The needle is inserted into the lumen of the vein and a quantity of blood equal to the solution in the syringe is withdrawn. The entire contents of the syringe is slowly injected. Kolle claims that the mixing with the blood immediately reduces the toxicity. In spite of the dark color of the solution, in a good light the blood withdrawn is easily seen:

In both these methods great care must be used that none of the solution escapes into the tissues, as it is extremely irritating.

Through the courtesy of the H. A. Metz laboratories, a number of clinics throughout the country received supplies of silver arsphenamine under the trade name of "Silver Arsphenamine," for trial. In the University of Pittsburgh Clinic we used the drug on unselected cases. Both the above technics were given a trial in an attempt to determine the maximum nontoxic dose. The results were well marked. At present, however, it is far too soon for us to give any idea as to the effectiveness of the drug.

More than 100 cases were given in dilute solution to the patients varying from 4 to 60 years and weighing from 36 to 166 pounds. Eleven reactions were noted after maximum doses of .25 gm. or .3 gm. had been administered to 20 patients. These reactions occurred 2 or 3 hours after injection, were of moderate severity and lasted several hours. Two cases showed after 3 hours, severe reaction with dizziness, severe headache, and prostration, lasting 12

hours. On account of these reactions, larger doses were not given by this method. Later the method of using the concentrated solution was tried in the way described. Beginning with doses of .2 gm. the dose was increased to .1 gm. each time until the women were given .35 and the men .4 gm. and only two reactions were noted. One had headache and a feeling of prostration  $\frac{1}{2}$  hour after administration, which lasted 15 to 30 minutes; the other was a reaction in a very nervous woman who always showed reaction regardless of dose or preparation used. Several cases had slight dizziness or mild headache which came soon after and lasted only a short while.

Thus, in our experience, the use of the drug in the concentrated solution first mixing with the blood is far superior to the other method.

We have been using silver arsphenamine once a week and in conjunction with mercury just as arsphenamine was used. We did so because reports received were not sufficiently good to justify following the manufacturers' plan of using it alone. A number of clinics have done this. By using it in the same way comparisons with arsphenamine are better.

At the Boston meeting, Parounagian reported over 4000 injections of silver arsphenamine and his is an enthusiastic résumé. He says reactions were few and results were extraordinary and he prefers it to the arsphenamine.

Fordyce, Rosen, and Goodman, in discussing the above work, supplemented recommendation, but Rosen gave two or three injections a week which raises the question: how much better would either drug be if the intervals of dosage were the same?

Hazen unqualifiedly condemned the drug. In his hands it was practically inert. In no case was the Wassermann reversed and several cases developed mucous membrane lesions while under treatment with silver arsphenamine. Major Walson in his paper gives a complete review of the European literature which is very favorable. Walson gave over 6,000 injections and is very reserved in his opinion as to the superiority. He believes the drug worth a very thorough trial and also says mercury should be given till it is definitely proved to be less useful.

As to the dangers of the drug, they are the same as those of arsphenamine and need not be mentioned here, save one, argyria. One



case is reported from Germany. Walson had none and had read of none. Nevertheless, when one considers that the drug contains 14 per cent silver and when one views the large quantity of brown silver solution entering the vein, the thought of argyria will always present itself and it must be considered as a possibility.

As a summary, we believe with Walson that silver arspenamine is worth a trial, but changes in the present mode of therapy, as discontinuing mercury, are hardly indicated by the present data on the drug.

The concentrate solution mixed with the blood before injection is much less toxic.

The real value of the drug in syphilis is yet to be determined. We believe the danger of argyria to be a great one and its appearance in any case would be sufficient to condemn the drug. Silver arspenamine, if it does not replace arspenamine, may be useful as an alternate drug in the treatment of patients who have an idiosyncrasy to arspenamine.

As has been mentioned, the reports as to the superiority of silver arspenamine over arspenamine are somewhat varied. Our impression is that it is not superior to arspenamine and in our work the aim was to increase the nontoxic dose to such a figure as would give the new drug a greater effect.

From our rather limited experience with the drug, comparing serological and clinical results with those obtained with arspenamine we believe that weight for weight silver arspenamine is more toxic than arspenamine and in the dosage ordinarily used, a less effective spirocheticide.

## PUBLIC HEALTH ACTIVITIES IN VENEREAL DISEASE CONTROL

BY H. H. HAZEN, M.D., WASHINGTON, D. C.

*Professor of Dermatology and Syphilology, Georgetown University, Professor of  
Dermatology and Syphilology, Howard University*

(Received for publication, April 7, 1921.)

WITHIN the past few years the knowledge of syphilis has been totally revolutionized by the discovery of the causal organism, of the Wassermann reaction and of arsphenamine. Twenty years hence we shall probably add a fourth discovery equal to any of the three, namely, the systematic control of the disease from the Public Health standpoint. The War, of course, forced the issue and taught us two things: first, the necessity of controlling venereal disease, and second, that the diseases could be controlled. Not the least among the agencies attacking venereal problems is the Division of Venereal Diseases of the United States Public Health Service. During the past year I have been fortunate enough to be in close touch with this Bureau and to see the important work which it is doing. The following activities may be mentioned.

### LEGISLATION

The officials of this Service are constantly studying conditions which are conducive to the spread of venereal diseases and have helped many states in preparing laws directed against such conditions. Data, literature and personnel has been made available to the State Boards of Health and this has resulted in the enactment and enforcement of necessary laws and appropriations of money for venereal disease control work by the States.

### EDUCATION

Some of the greatest work has been done in educating both physician and laity. It cannot be emphasized too strongly that the

Public Health Service is not attempting to displace the efficient treater of venereal disease but is absolutely opposed to the nostrum vender, whether this man is the frank seller of fake cures, the advertising self-styled specialist, or the president of the local county medical society. The Public Health Service invariably advocates that people go to reputable physicians. No attempt has been made to socialize the treatment of venereal disease. The honest physician will always receive help and not criticism, the only demand is that he make himself efficient.

One of the greatest attempts to educate the physician was the Institute on Venereal Disease Control and Social Hygiene held in Washington from November 22, to December 4, 1920. Four full courses comprising the "Diagnosis and Treatment of Syphilis," the "Diagnosis and Treatment of Gonorrhea," "An Advanced Course in the Treatment of Syphilis and Gonorrhea," and "The Delinquent and the Law" were given. Half courses were given on "The Psychology of Delinquents," "Sex in Education," "Protective Work for Girls," "Clinic Nursing and Social Work, Heredity and Eugenics," "Sociology and Social Hygiene," "Methods of Public Education," "Sex Psychology, and Clinic Management." Clinics were also held in connection with the Institute. Among the well-known V. D. men on the program were Fordyce, Keyes, Norris, Hugh Young, Geraghty, H. A. Fowler, and Irvine. It would be out of the question to mention the faculty giving the other courses but the best known educators in the country responded willingly, and gratuitously. Over 600 persons attended the meetings and there can be no doubt but that the affair was a success. Scores of letters have been received highly commending the work. Plans are now being made for similar, but less ambitious, institutes to be held in the future in various other cities of the country.

The Public Health Service has aided the local and state health officers by starting a large number of venereal disease clinics, giving both financial aid and personnel.

There is also a monthly abstract of the more important literature prepared and sent out to those who are interested.

Special attempt has been made to educate the physician as to the necessity of reporting all cases of venereal disease to the state health authorities, these reports being made in most states by num-



ber and not by name, unless the patient refuses to take treatment, or shows a disposition to become a menace to the community at large. The writer can see no objection to the report of cases in this manner. The large attendance at the various local venereal disease dispensaries would seem to show that the patients are not nearly so solicitous in regard to secrecy as many of the physicians are. The only objection that the authorities have heard made to the report of cases is that the patient will fear publicity.

In regard to the laity, a large amount of quiet work has been done, and there is a very efficient division for public education which is constantly holding conferences with educators and those interested in social hygiene movements; their object being to educate adults and young people. As an illustration may be mentioned the suggestion to have the children taught the principles of sex hygiene through biology and hygiene in schools.

Various open meetings have been held both for military and private persons. In the city of Washington one of the public health men is spending most of his time in arranging meetings in connection with the local Hygiene Association, and the Health Department in getting meetings for public instruction and in providing speakers for various other clubs and associations. A number of films have been prepared and can be obtained for use at various approved meetings. In addition to films, many placards of advice have been installed in various places; witness them in railroad train toilets. Special exhibits, arranged according to age and sex of those who are to see them, have been prepared and thoroughly tried out. Many excellent booklets upon sex education are also available.

Another important piece of work which the Public Health Service has done is the testing of all arsphenamine before it is released by the manufacturers for public consumption. These tests are extremely rigorous and many valuable articles have been printed concerning the toxicity of arsphenamine as the result of them.

## DILUTE OR CONCENTRATED SOLUTIONS OF ARSPHENAMINE

BY DOUGLASS W. MONTGOMERY, M.D., AND GEORGE D. CULVER, M.D.,  
SAN FRANCISCO, CAL.

(Received for publication, March 14, 1921.)

A SHORT time ago, in speaking with a man whose practice is largely the treatment of syphilis, he remarked that, although he gave a great many infusions, it was rare to have them followed by any disagreeable symptoms, and he attributed his good fortune to diluting well his medicament. It may be remarked in passing that it was very important for him not to occasion trouble, as almost all the infusions given by him are administered in the office.

Even in 1910 the difference existed between those who employ dilute and those who employ more concentrated solutions of arsenobenzol. One of us was in Frankfort at this time, and was advised to visit the clinics of Weintraud in Wiesbaden and Scheiber in Magdeburg. In Wiesbaden the drug was given very dilute and by the gravity method, and in Magdeburg in more concentrated solution and with a syringe. The syringe, however, was a large substantial affair holding a considerable quantity of fluid. With the increased solubility of the drug the syringe has been reduced to the proportions of an ordinary hypodermic instrument. Is there practically any difference between these two methods, or is one preferable to the other?

The first infusions we gave were with the large German syringe as employed in Magdeburg, and we had a number of disagreeable experiences, partly, it must be said, due to the drug itself, which was not then as well prepared as it is now, and partly we think, to the concentration of the solution. We finally abandoned the syringe for the gravity method, and now we not alone use one hundred c.c. of water to dissolve the full dose of medicament, but we follow the infusion of the drug by the infusion of an equal quantity of normal salt solution. This technic was hit upon quite by accident. After the arspenamine solution had run out of the receptacle we were in the habit of pouring in salt solution to drive through the small quantity of medicament still left in the rubber tube. Frequently, more than enough to ac-

comply this would flow through, and it was noticed that these patients, with whom this happened, were remarkably free from consequential disagreeable symptoms. Finally this procedure was adopted as a part of our technic.

We allow the fluids to flow in quite slowly; it takes about ten minutes to accomplish this, and we regard the ten minutes as being well spent.

The above subject is a most important one. We medical men now are employing such powerful chemical and physical means to attain our results, that the avoidance of all accidents is absolutely impossible. We, therefore, it seems to me, for our own comfort and peace of mind and for our good name, should take all the precautions necessary. We must always remember that an unfortunate result attributed to us, or even to a druggist, is associated in the public mind as against all of us.

#### ADDENDUM

##### AN ANAPHYLACTOID REACTION

We had scarcely sent off the above note on our success with our technic when we suffered an experience calculated to shake our pride.

We had been treating for some time a strong healthy man of thirty-nine years of age, who had acquired his infection eleven years previously, and who had proven extraordinarily refractory as regards his Wassermann reaction. We were giving him a series of neoarsphenamine infusions and grey oil injections. We had already given the patient three infusions of this series, of which the last one was given fourteen days before. He had always stood the infusions well, and after receiving them had gone home in his automobile several miles into the country.

On the occasion in question the full dose (0.9) had already run in, and we were following it with salt solution according to our custom, when suddenly the attack came on.

The patient said, "I never felt like this before, I have a peculiar feeling and I can't see." The face flushed, the ears became blue, the eyes injected and the patient's expression was anxious, he became nauseated and he repeated over and over again in a low moaning voice, "Save me, save me." His heart and pulse kept up wonderfully well considering the evident disturbance of the peripheral



vascular system and of the nervous system. After a period of effacement the patient endeavored to struggle to his feet, but fell back helplessly. He told us afterwards that for a time he completely lost his sight, but not his consciousness. As he lay moaning, his nose grew waxy pale and pointed and I thought we were going to get the Hippocratic face. The attack lasted about fifteen minutes, after which he got up and went home on the train.

This was an instance of one of a number of arspenamine reactions that Homer Swift has called anaphylactoid reactions, a very rare occurrence, and the first case in our experience. It is recommended to give adrenalin, and certainly it requires a good deal of strength of mind to desist from giving something. I think, however, that in such cases it is wise to be conservative in the employment of powerful drugs. The constitution is evidently struggling with a great load, and an addition to this may be fatal.

It is also recommended to give atropin as a prophylactic previous to administering the next dose of arspenamine.

In this case we determined not to give a "next dose," at any rate, until after the lapse of a very considerable time.

The above incident cannot, as far as we can learn, be ascribed either to a fault in the drug, or to its manner of administration. It comes on, as do the other anaphylactoid reactions, independently of any precaution the physician may take. It most frequently occurs when a dose or a number of doses have been given a short time previously.

# Abstract of Current Syphilis Literature

It is the purpose of this JOURNAL to review so far as possible all literature on syphilis as it appears in other medical periodicals and to present it in abstract form. Authors are requested to send abstracts or reprints of their papers to the Associate Editor, Dr. Wm. H. Deaderick, Dugan-Stuart Bldg., Hot Springs National Park, Ark.

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WM. H. DEADERICK, M.D., EDITOR

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## **Syphilitic Placentas and Phagocytosis of the Treponema.**—Manouélian (Paris). *Gynecologie et Obstetrique*, January, 1921, iii, 1.

In this brief report of work done in the Pasteur Institute the author attempts to answer the question "why is the treponema so seldom found in the placenta?" This answer is as follows: in the fetal placenta there exists an intense phagocytosis by the mobile cells of this structure. The following cells take part in this process—macrophages, polynuclear neutrophiles and eosinophiles of the blood as well as fixed cells (endothelia of the capillaries). The author's microphotographs show very few treponemas free in the vessels and their walls or in the fetal portion of the placenta. Most of these parasites lie enclosed in the cytoplasm of the cellular elements above named. The changes may be studied from typical treponemas to moniliforms, forms *en rouleaux*, granules, etc., to the final state of spirochetolysis. An interesting fact is that these transformations take place in the finest ramifications of the capillaries, including those of the chorionic villi. The author has never seen them in vessels with calibres of notable size. In contrast with the placenta the liver swarms with treponemata. We can now comprehend why the fetus may contain an abundance of the latter in a state of proliferation while the placenta is almost immune.

## **Immunity Studies in Experimental Syphilis.**—Frederick Eberson, St. Louis. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 775.

The infectivity of *Spirochete pallida* derived from old lesions was not diminished by prolonged residence in an infected focus. No correlation seemed to exist between the period of incubation of the organism, on one hand, and the age of the lesion from which it was obtained, on the other. Survival of *Spirochete pallida* in experimental syphilis was subject to marked variation. The persistence of spirochetes in rabbits' testicles was not correlated with the period of incubation, with the age of the lesion, or with the number of animal passages of the different strains studied. Incomplete observations show that they may be present for more than five months. Spirochetal content of lesions in the testicle

was not correlated with the age of lesions and survival within the focus of infection. Fresh as well as old spirochetes did not appear to influence adaptation to environment as measured by survival, or to affect the period of incubation. No differences have been found to exist between different "lines of descent" made from a series of animals which represented transfers from actively developing lesions, and a series of generations which were derived from animals having old regressive lesions. Although syphilitic manifestations in the rabbit testicle may exhibit a wide range of variability in their cyclic changes, certain outstanding features may be associated with definite strains of *Spirochete pallida*. A chronic proliferative type of reaction characterized organisms which had been isolated originally from cases of latent syphilis. The type of lesion, however, did not give an indication as to the fate of *Spirochete pallida* in such lesions. Serotal lesions following as late manifestations of old testicular infection were not referable to particular strains. Elaboration of syphilitic antibodies appeared to be at a maximum late in the course of infection and predisposed to a condition of latency in which, despite the absence of lesions, *Spirochete pallida* could be demonstrated. Far from preventing reinoculation with *Spirochete pallida*, a state of resistance appears to favor the localization of organisms in tissues without giving rise to manifest lesions. Inoculated testicles which remained negative for indefinite periods, presenting no lesions, and proving negative by puncture, have been found to harbor *Spirochete pallida* capable of infecting other animals. The tendency for a condition of latency to occur was confined to certain strains of organisms, in particular those which had been isolated from latent sources in patients and rabbits. In the absence of lesions and with negative dark-field findings over a period of four to five months, *Spirochete pallida* was isolated from apparently normal testicles which had previously been positive for spirochetes. Sensitization phenomena may play an important part in the production of a certain kind of serotal lesion resulting from autoinoculation of a normal testicle, from experimental infection of the opposite testicle in the course of involvement of the other, or from old testicular foci. Seven strains of *Spirochete pallida* have been studied from the standpoints of infectivity and survival and differential characters. Five of the strains were isolated from cases of latent syphilis—inguinal glands and semen—and the others were obtained from penile chancres.

**A Study of Nissl's Staebchenzellen in the Cerebral Cortex of General Paresis, Senile Dementia, Epilepsy, Glioma, Tuberculous Meningitis and Delirium Tremens.**—U. Noda, Kioto, Japan. *Journal of Nervous and Mental Disease*, 1921, vol. liii, p. 161.

This study is based upon twenty-one cases of cerebral disease, ten of general paresis, six of senile dementia (accompanied with more or less arteriosclerosis), one each of epilepsy, delirium tremens, and tuberculous meningoencephalitis, and two of glioma. Some of the findings lead to rather positive conclusions, others await still further investigations. The results of this study may be summarized as follows: A great number of staebchen cells are exhibited in all of the ten cases of general paresis. Staebchen cells are of great significance for the histopathological diagnosis of the general paresis of the insane. Staebchen cells are also



found in the cortex of meningoencephalitis, but never so numerous as in general paresis. The two cases of glioma have displayed numerous staebchenlike glia cells in the tumor tissues, and also a moderate number in the cortex, especially in the area where glial proliferation has been marked. In the remaining cases (epilepsy, delirium tremens and senile dementia), only a few staebchen cells were found and these apparently were of no pathologic significance. Staebchen cells show a certain relation to pathologic alterations in various central nervous diseases, especially to the alterations in mesodermal and ectodermal elements. Staebchen cells have a multiple genesis, some from mesodermal cells, others from glia cells. Some staebchen cells occasionally immigrate from the pia to the cortex, at least this was shown in a case of tuberculous meningoencephalitis.

**Syphilitic Backache.**—Joseph Victor Klauder, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 761.

Syphilitic backache is classified as a symptom of syphilitic involvement of the spinal cord, lumbar muscles and vertebræ. In the majority of instances, it is a symptom of spinal cord syphilis. Syphilitic backache, a symptom of syphilis of the spinal cord, is meningeal in origin and due to irritation of the posterior sensory roots. This involvement may be acute, subacute or chronic, and may be present from the exanthematous period of the disease until many years later. The symptom backache is a part of the meningeal syndrome. These symptoms in general are essentially the same as those in other forms of meningitis: pain, which may exist between the shoulders or in the back, paresthesias, painful sensations and acute attacks of girdle pain which radiate anteriorly around the lateral part of the chest. Hyperesthesia is sometimes present, and the tendon and skin reflexes are increased. In addition, there are symptoms of motor irritation. Backache, stiffness and tiredness are the chief complaints of the patient. Clinically, in addition to these neurologic abnormalities, there is rigidity of the back, combined with localized tenderness on percussion of the vertebral column. Other objective evidences of neurosyphilis are usually present, since an isolated involvement of the spinal cord is exceptional. The usual spinal fluid findings in this condition are given. Case histories illustrating this type of syphilitic backache are presented. A plea is made for a thorough history and clinical examination of every syphilitic in order that treatment may be administered in the meningeal stage of neurosyphilis rather than in the parenchymatous stage. The backache which is sometimes present in acute secondary syphilis is placed under this heading, although it is a toxic expression of the acute spirochetemia rather than syphilitic myositis. Syphilis of the muscles is discussed and various clinical types are presented. A syphilitic involvement of the vertebræ is usually seen in the cervical rather than in the lumbar region. A brief review of the literature of syphilis of the vertebræ is given. Syphilis is more likely to affect the spinous and transverse processes than the bodies of the vertebræ. The pathology of this condition is given. "Cold abscess" formation, which is usually present in tuberculosis, is considerably less likely to be encountered in syphilis. In the symptomatology of this process there is no characteristic symptom which serves to distinguish it from other pathologic conditions of the

spine. A secondary involvement of the spinal cord and its membranes is less likely to occur in syphilis than in tuberculosis. Syphilis may activate latent tuberculosis. This possibility must be considered in the presence of a pathologic involvement of the vertebræ in a syphilitic. The therapeutic test in these cases is not conclusive since tuberculous lesions in a syphilitic are improved after antisymphilitic treatment. A case history is given in which the necrosis of the lumbar vertebræ was probably tuberculous rather than syphilitic. Backache may also be caused by a synovitis of the spinal joints. This involvement is the commonest lesion in syphilis of the spine. The syndrome of the process is this: Deformity, when present, is seen in a prolongation of the dorsal curve into the dorsolumbar region, where normally a concavity exists, or a flattening. There is a localized stiffness, at first due to spasm, and later to adhesions. Hypotonicity of the ligaments and muscles of the sacro-iliac joints and hips is a predominating symptom.

**Syphilis of the Trachea and Bronchi: A Résumé of the Diagnostic Features, With Three Case Reports.**—Philip Moen Stimson, New York. *American Journal of the American Sciences*, 1921, vol. clxi, p. 740.

In syphilis of the trachea and bronchi the characteristic symptoms are those of tracheal or bronchial obstruction; that is, (1) a peculiar type of dyspnea with labored, prolonged inspiration and shorter, easier expiration; (2) paroxysms of excessive dyspnea, sufficient to cause syncope or even death; (3) cough, which is usually hard, brassy and paroxysmal, though quite variable in character; (4) stridulous sounds, particularly during inspiration; (5) frequently an inspiratory sinking-in of the tissues of the root of the neck, epigastrium and lower intercostal spaces; (6) other features, such as more or less profuse sputum, a limitation in the mobility of the larynx, etc. Wide variations from this symptom-complex, however, are not uncommon.

**Late Hereditary Syphilis.**—Mariano R. Castex and Delfor Del Valle, Jr., Buenos Aires, Argentine. *Surgery, Gynecology and Obstetrics*, 1920, vol. xxi, p. 160.

Hereditary syphilis is a very frequent cause, perhaps the most frequent, of membranous perenteritis and analogous conditions. Its pathogenesis is complex as several factors operate, which set down in chronologic order are: defects of conformation in the intestinal walls because of the faulty endocrine function which presides over and governs their development. These malformations on the one hand, and the abnormal function of the nervous system (sympathetic and autonomous), owing to the endocrine deficiencies, produce defects in the gastrointestinal statics and dynamics. As a consequence of the latter we have intestinal stasis which brings on chronic inflammation of the colon. From the wall of the colon the inflammation spreads to the surrounding serous membrane, aggravating the existing congenital lesions. The primary cause of all this is hereditary syphilitic infection, generally in the form of a late manifestation. These cases, first of all, should be given

mixed antisyphilitic treatment with mercury chiefly. The surgical treatment is not to be abandoned, but is to be restricted to cases in which definite indications confirmed by clinical and radiologic diagnoses point to mechanical alterations of importance (kinks, adhesions, etc.); or to co-existing inflammatory lesions of adjacent organs: ovaries, tubes, appendix, gall bladder, duodenum, and stomach. Surgical treatment should consist in separating membranes and in molding and mobilizing the peritoneum, together with careful peritonization and removal of the adjacent affected organs. There is the group in which the patient suffers from the chronic abdomen and yet there is no anatomical lesion of importance. These should be considered as types of "sympathicopathy," owing to the particular deficiencies, more or less marked, of the endocrine glands as suprarenal capsules and thyroids, principally. It is important to know this type of chronic abdomen, for it involves a prognosis and a therapeutic management very different from the membranous perienteritic type. The prognosis depends on the anatomic and clinical type, and the period or stage of the affection: good, in cases of early diagnosis and rational treatment; less favorable, in those of late diagnosis where rational treatment is impotent in modifying chronic lesions already well developed. In these a more or less pronounced improvement is to be obtained by carrying out suitable surgical treatment.

**Syphilitic Iritis.**—Ernest L. Zimmermann, Baltimore. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1818.

Both in early secondary syphilis and subsequently in the course of the disease, the negro is more liable to iritis than is the white man. Iritis occurs in more than 10 per cent of all cases of early secondary syphilis in the negro, and is most often associated with follicular syphilides. Abnormalities in the cerebrospinal fluid of partially treated syphilites with iritis occur with no greater frequency than in the fluids of treated patients who have not had iritis.

**Syphilis of the Lungs Simulating Tuberculosis.**—Henry M. Minton, Philadelphia. *New York Medical Journal*, 1921, vol. cxiii, p. 813.

The frequency with which these cases appear at the Phipps Institute causes the author to conclude first, that syphilis of the apices of the lungs is not by any means a rare condition, and that there are many cases of this disease being treated for pulmonary tuberculosis. Second, that they should avail themselves more frequently of Wassermann and other blood tests in private practice in cases giving signs and symptoms of active tuberculosis, but not giving positive sputum. This should be done whether a history of a primary luetic lesion is obtainable or not, realizing that syphilis is often innocently acquired. Signs of an aortitis, of a perihepatitis, of weak or suppressed breath sounds, should make us suspect syphilitic infection. By pursuing such a practice there is no doubt that we will arrest some cases which are running a rapidly downward course.



**Delayed Manifestations of Syphilis.**—Harold Spence. *Lancet*, London, 1921, vol. cc, p. 908.

There is ground for the belief that in association with an exciting cause a suitable soil is necessary for the production of chronic gastrointestinal ulceration. Physical, chemical, or bacterio-chemical excitation is a recognized factor in the development of later specific morbid processes elsewhere, familiar examples being the incidence of glossitis in the smoker and the gummatous ulceration due to traumatism from an ill-fitting truss; and from the general trend of evidence and our knowledge of the morphology and pathology of syphilis we will not be far astray in assigning to it a more important role in the etiology of gastroduodenal ulceration.

**Involvement of Nervous System During Primary Stage of Syphilis.**—Udo J. Wile and Clyde K. Hasley, Ann Arbor, Mich. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 8.

Deviations from the normal in the spinal fluid of 221 cases of syphilis in which only the chancre was present was found in forty-nine cases, or 22 per cent of the cases examined. Increase in globulin and albumin virtually parallel was the most constant of the abnormal findings, occurring in twenty-five of the forty-nine cases. Pleocytosis was the next most frequent finding, occurring in twelve cases. The positive Wassermann test in the fluid occurred less frequently than the other two findings, being present in but eight cases. Within certain limitations any single one of the above-mentioned deviations from the normal occurring alone must be regarded as evidence of early central nervous system involvement.

**Unusual Location of Extensive Pigment Syphilides.**—Gravagna. *Annales de Dermatologie et de Syphiligraphie*, 1921, vi. 2.

The author first alludes to the familiar type of pigmentary syphilide, small, confluent, but interspersed with areas of clear skin and polycyclic margins. This type named by Hardy *leucoderma syphiliticum* was limited very largely to the sides of the neck. Later observers indeed found the same type of syphilide in various other localities. It was also learned that the apparently sound skin in the meshes of the reticulum was in reality achromic, the entire lesion amounting to a regrouping of the pigment into deeply pigmented and pigmentless skin. The author's case has hardly anything in common with the preceding. The location was the hand and the pigment occurred in a continuous broad sheet. The patient, a man of 24, had had syphilis for about 8 months and had been treated with injections of biniodide of mercury. The primary and secondary lesions had all vanished before the appearance of the pigmentation. This first manifested itself after about four months of latency and upon the dorsal aspect of the hands. It appeared suddenly and without the operation of any factor. The stains suggested ink spots and caused him so much annoyance that he began to wear gloves. The author examined him at this juncture and found him in excellent general condition. The only

evidences of past syphilis were the scar of the chancre and polyadenopathy. An illustration shows that while in the right hand the thumb, index and medius with the metacarpal area were covered with pigment the condition was reversed on the other side, where the ulnar half of the hand alone suffered. The Wassermann was positive. The syphilitic nature was shown by the disappearance in three weeks of the discoloration under intensive mercurial treatment.

**Aortic Lesions in a Heredosyphilitic.**—M. Pinard (Paris). *Bulletin de la Société Française de Dermatologie et de Syphiligraphie*, 1921, 2.

This case is atypical and while there is syphilitic heredity the ascendants and family are so much infected with the malady that the exact transmission cannot be shown. The patient, a woman of 40, was of good personal history and only recently had she presented evidence of disease which proved to be aortic. Before this period she had complained of dizziness and a routine examination had disclosed a positive Wassermann. Although placed on an intensive cure her thoracic symptoms became aggravated. The heart beat was in the sixth interspace, the aorta was dilated and the x-ray showed that the dilatation involved the entire vessel. An Argyll Robertson pupil was noted as present. It was now remarked that the dentition was very poor while certain stigmata of degeneration were found. The family history brought out the fact that the patient and one sister are the only survivors of nine gestations or since one of the latter was a twin pregnancy, of 10 children. In reality there had been six abortions or miscarriages and one stillborn twin, the other twin living to the age of 7, but as an idiot and also blind. The patient had but one gestation soon after marriage and aborted, while the sister had borne two children, one dying in infancy and the other living, but a cripple. The sister herself suffered from recurrent gastroenteritis and was also a Wassermann positive. The parents of the two sisters were cousins and probably both syphilitic although proof was lacking. Three of the four grandparents presented affections which might have been syphilitic—heart disease, apoplexy, disease of the thorax, while the fourth died at 40 after a life of "high living." It was impossible to trace the pedigree of the disease in such a family.

**Benign Gastric Ulcer in a Known Syphilitic.**—W. Frank Fowler, Rochester, N. Y. *Surgery, Gynecology and Obstetrics*, 1921, vol. xxxii, p. 419.

Organic gastric syphilis is more frequent than formerly supposed. The gross lesions of gastric syphilis are (1) gummata in various forms, and (2) diffuse infiltration. Specific ulcers result from the degeneration of gummata. Symptomatically such lesions differ from benign ulcers chiefly in the absence of pain, ease from food and alkalis, less periodicity, anacidity, vomiting with good appetite, excessive weight loss and improvement in gastric function with specific treatment. Without operation the diagnosis usually rests upon a past history of early syphilis, present late syphilitic signs, Wassermann reactions and the therapeutic test. However, a negative Wassermann reaction does

not exclude the possibility of gastric syphilis, and benign lesions of the stomach may occur in a known syphilitic. At operation specific ulcers are always multiple, ragged lesions occurring usually at the cardia, the lesser curvature, or the pyloric region accompanied often by perigastric adhesions, thickened gastric walls, and gastric deformity. Large gummatous tumor masses or cicatricial contractions subsequent to extensive ulceration simulate carcinoma, particularly as regards the type of dyspepsia, the vomiting, the rapid weight loss, and the anacidity, although the cachexia and loss of strength are less than that encountered in malignancy and the course may have been longer. The operative findings consist, usually, of an irremovable gastric tumor mass indistinguishable from carcinoma. The x-ray evidence also simulates carcinoma. The roentgenographic signs of organic gastric syphilis in general consist of encroachments upon the lumen, distortions, and deformities. The microscopical evidence consists of the characteristic syphilitic obliterative endarteritis and perithelial lymphocytic infiltration with atrophy of the mucous membrane and hypertrophy of the submucosa and the muscularis. Postmortem confirmation of the diagnosis is infrequent. Organic gastric syphilis may simulate (a) benign gastric ulcer, (b) gastric carcinoma, or (c) present an atypical gastric picture. The diagnosis of organic gastric syphilis is often difficult and sometimes impossible. A negative Wassermann reaction does not disprove the existence of syphilis and a positive reaction does not prove that a gastric lesion is specific. The "therapeutic test" is usually reliable but not infallible. The roentgenographic evidence is not conclusive. Exploration may not be determinative, particularly as regards differentiation from carcinoma. Atypical, chronic gastric disorders which are unresponsive to the usual treatment should arouse suspicions of syphilis.

**Asthenias Due to Pluriglandular Disorders of Syphilitic Origin.**—Merklen, Devaux and Desmouliere (Paris). *La Presse Médicale*, Feb. 16, 1921, xxix, 14.

The manifestations of syphilis are not necessarily objective and may comprise purely subjective states such as asthenia. This knowledge is naturally due to serodiagnosis. Women especially are apt to complain of an unmotivated sense of prostration which may be continuous or intermittent and vary more or less in degree. Ordinary therapeutic resources are used in vain. The condition passes for one of nervous invalidism. The usual resources such as visiting or change of residence brings about only a transitory amelioration, and a crisis may occur in the midst of such a change. The authors do not claim to have first discovered this morbid state for it has been described under the name of syphilitic neurasthenia. But the latter when secondary to another process is practically an organic affection. To what system then shall we attribute it? In the present state of our knowledge we are apt to think of the endocrine glands and especially of the adrenals. We know that congenital syphilis may act destructively on these bodies and set up dystrophies. This has been shown by Hutinel among others. It is reasonable to suppose that in the acquired syphilis of the adult, something of the same nature may occur.



Asthenia attends on various clinical expressions of secondary syphilis but we are not interested in the asthenia which accompanies outspoken lesions but solely in this connection in a form which appears *d'embliée*. This appears at some time during the evolution of the disease and indicates that the virus when in its viable state has done some damage to one or more of the endocrine glands. The blood of these patients gives a Wassermann positive of feeble character. The interesting question of prognosis is answered by the claim that specific treatment ameliorates and if persisted in may cure.

**Elephantiasis with Reference to Syphilis.**—Joseph Lintz, New York. New York Medical Journal, 1921, vol. cxiii, p. 535.

Direct evidence of the filarial origin of elephantiasis has never been fully demonstrated. Three cases are presented of unilateral enlargement of a limb due to syphilis. One case quite definitely and two cases very suggestively resemble elephantiasis, the pathologic lesion of which is probably an endolymphangitis. The two cases treated responded to the therapeutic test, though not yet completely cured. It is suggested that all cases of elephantiasis be exhaustively examined for evidence of syphilis, and that intensive anti-syphilitic treatment be tried. This is especially desirable because of the otherwise almost hopeless prognosis.

**The Wassermann Reaction: Results of Two Methods Compared.**—J. S. K. Boyd, R.A.M.C. Journal of the Royal Army Medical Corps, 1921, vol. xxxvi, p. 344.

The technic of a method of performing the Wassermann reaction detailed in a Ministry of Health report is briefly compared with one of the accepted standard methods. This technic is adapted to Donald's dropping method of distributing the reagents. The results of 150 sera tested simultaneously by both methods are compared. It is found that the Ministry of Health method gives a much larger proportion of positives and partial positives in cases of syphilis which have received a course of treatment than does the other method. The possibilities of this in the control of treatment are discussed.

**A Simple Quantitative Serum—Reaction for the Diagnosis of Syphilis.**—Georges Dreyer and Hugh Kingsley Ward, Oxford, England. Lancet, London, 1921, vol. cc, p. 956.

The reaction for the diagnosis of syphilis described has yielded in the author's hands diagnostic results that compare more than favorably with the Wassermann reaction as carried out in this country. The results obtained are quantitative as well as qualitative. The reaction can be Standardized, and the results can therefore be expressed in standard units, thus allowing direct comparison of the results obtained by various workers. It is, therefore, possible to follow accurately the changes in the unit-content of the serum in a case of syphilis under treatment, and in this way to ascertain whether clinical improvement is regularly accompanied by a fall and an exacerbation

by a rise in the unit-content of the serum. This important point once settled, it will be possible to compare accurately the relative merits of different methods of treatment.

**Is There an Active Nervous Syphilis without a Meningeal Reaction?**—C. Vincent (Paris). *La Médecine*, February, 1921, ii, 5.

By meningeal reaction the author indicates a positive cytological find in the cerebrospinal fluid along with hyperalbuminosis and positive seroreaction. One knows that at a given moment there may be no positive evidence of this sort and in old tabetics there may be a normal punctate along with a rigid pupil and other classical symptoms. The fallacy lies in the gratuitous assumption that there has not been or will not be a change in this respect. There may be an exacerbation of the disease accompanied by the meningeal reaction. In doubtful cases we must first make certain of the diagnosis of syphilis. In the case of a man of 53 of recorded syphilitic antecedents there appeared 7 years after the chancre symptoms which suggested incipient nervous syphilis (tabes?). The spinal puncture was not made until the lapse of another year when it was found to give a full positive result. The man served throughout the war as engineer and was only slightly bothered with paresthesia, which did not become aggravated. Not until 1918 did ophthalmoplegias appear, to vanish again under intensive treatment. In 1919 the lumbar punctate was normal but soon after the test there was a sudden paralysis of the left lower extremity. The symptoms suggested both polyneuritis and early tabes (girdle sensation, etc.), although the latter were vague. They improved under intensive mercurial treatment. Still another relapse has occurred to date but the subject is at present symptom-free. The spinal punctate seems never to have given a positive test since the one last mentioned. The author after narrating a similar case concludes that absence of meningeal reaction such as undoubtedly occurs in the single examination does not imply that there never has been a positive reaction but the reverse; and that in the great majority of cases the reaction persists throughout.

**Report of 5,000 Wassermann Tests with Observations.**—E. T. Manning, Omaha. *Nebraska State Medical Journal*, 1920, vol. v, p. 170.

A negative reaction may or may not be of significance. If there is an active process under suspicion, such as an ulcer, a rash, or enlarged glands, then a negative result practically rules out syphilis; however, if the lesion is in the nervous system, then a negative reaction is not at all conclusive. Parenthetically it may be stated that some additional assistance in the case of syphilis of the nervous system is usually obtained by doing a Wassermann test on the spinal fluid. A one-plus reaction must be considered in conjunction with the clinical picture. If the case is of nerve origin it is of added significance. If it is an old treated case or if there is a history of a suspicious primary lesion some years preceding, it is of value. If the reaction is false, another test will usually prove negative. A two-plus reaction is common in insufficiently treated cases—in the very early cases shortly before the appearance of the rash—in all latent cases, and in syphilis of the nervous

system such as tabes or paresis. A false two-plus is very unusual. Regarding a three-plus reaction, it may be mentioned that many workers do not use a three-plus designation, including it under a four-plus reading. It has seemed to the author that by using three antigens he was able to separate a four-plus where there is complete inhibition of hemolysis from a two-plus where there is no hemolysis with the cholesterin antigen, but where there is almost complete hemolysis in the other two he has found the reaction to occur in latent or partially treated syphilis. It may be regarded as denoting a sub-acute infection. The reaction practically always means syphilis. A four-plus reaction means in his terminology complete absence of hemolysis in all antigens. With almost no exception it means syphilis. In conclusion, it should be remembered that a negative reaction does not necessarily mean absence of syphilis, but that a three- or four-plus Wassermann reaction nearly always spells lues.

**Results of the Wassermann Test on 1518 Men at San Quentin Prison.**—G. W. Nagel San Quentin, Calif. *California State Journal of Medicine*, 1921, vol. xix, p. 193.

The Wassermann test should be made a routine procedure in all complete medical examinations. A negative history and physical examination does not preclude the possibility of lues being present. The treatment as outlined is an effective and practically safe method of bringing about a negative Wassermann reaction. Five or six injections, accompanied by mercury rubs extending over a period of from one to two years are usually sufficient to bring about the desired result. A small percentage of cases show no improvement in spite of prolonged treatment.

**Wassermann Test With Secretions, Transudates and Exudates in Syphilis.**—Joseph V. Klauder and John A. Kolmer, Philadelphia. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1635.

The Wassermann test was performed with milk, saliva, seminal fluid, exudates and transudates from syphilitics. An antisheep hemolytic system water-bath incubation and a cholesterolized antigen were used in performing the test. Wassermann tests with the heated serum of each patient were conducted with the same antigen and with the same technic. All yielded a positive reaction. All specimens were first titrated for anticomplementary activity. Milk and saliva were found to be highly anticomplementary. Nineteen specimens of milk were examined; positive Wassermann tests were obtained in three. Twenty specimens of saliva were examined; a weakly positive Wassermann test was obtained in one. Thirty specimens of seminal fluid were examined. A moderately positive Wassermann test was obtained in one. Ten specimens of aqueous fluid from the anterior chamber of the eye were examined. All yielded a negative test excepting two in which the test was doubtful. Eleven specimens of exudates and transudates were examined. All yielded a positive Wassermann test. The degree of positive Wassermann reaction closely paralleled the reaction obtained with blood from the same



patient. Evidence is presented which supports the belief that the complement-fixing antibody in spinal fluid is in all probability dual in origin, neural as well as hematogenous. The presence of the complement-fixing antibodies in exudates and transudates from syphilites is regarded as derived from the plasma of the blood. The Wassermann test was performed with the surface fluid from a number of chancres, and with the saline extract of syphilitic nodules removed from the testicles of syphilized rabbits. All the tests performed with chancre fluids yielded almost uniformly four-plus reactions. The reaction performed with saline extract of syphilitic testicular nodules yielded positive results. The control reactions in both studies were negative. These positive reactions support the belief that at the site of syphilitic lesions there may occur a local formation of complement-fixing antibodies. The reaction in these circumstances is styled the "local" Wassermann test. The practical value of the "local" Wassermann test is pointed out as a possible aid in differentiating syphilitic from nonsyphilitic lesions, particularly when applied to chancre fluid as a means to the early diagnosis of syphilis.

**Absorption and Elimination of Mercury in the Different Methods Used in the Treatment of Syphilis.**—Svend Lomholt, Copenhagen, Denmark, *British Journal of Dermatology and Syphilis*, 1920, vol. xxxii, p. 353.

It has been discussed widely whether mercury in the infected body acts directly upon the spirochetes or more indirectly on the human organism by stimulating the bactericidal forces in it. Of these theories the latter is to be preferred in the author's opinion. Eighteen examinations of blood from patients under full mercury treatment or severely intoxicated with this metal have shown that the average content of mercury amounts to 1 to 2 mgrm. only per litre and never exceeds 3 mgrm. This concentration is so feeble that it makes a direct bactericidal effect very improbable. Moreover it was found, as the result of some investigation made in collaboration with Dr. A. Kissmeyer, that a colony of spirochetes grew well in horse-serum containing 5 to 10 mgrm. HgCl per litre and still distinctly in serum containing 20 mgrm. per litre. Under these circumstances the aim of the treatment must be to avoid all intoxications in order to avoid damage to the body and its bactericidal forces, but at the same time to maintain a sufficiently high permanent concentration of mercury in the organism without risking an intoxication. One has to remember that during administration the slow elimination allows an increasing accumulation of mercury in the body. But under a regular moderate supply the elimination can after a time reach an amount sufficient to establish a balance of absorption and elimination, a balance which, if sufficiently high, is eminently suitable for combating the disease. In order to obtain the required saturation of the body more quickly it is of advantage to make the supply of mercury somewhat larger at the beginning of the cure than afterwards. As to the question of the daily amount of mercury which can be considered sufficient to cover the daily consumption (saturation plus elimination), this amount can probably be estimated at 6 to 10 mgrm. per

day according to the size and tolerance of the patient. Therefore the aim must be to find just such methods of treatment as will provide a sufficient and regular supply to the organism. The curves of elimination of the different methods of mercury treatment show that this can be obtained by inunctions, by small, numerous injections of soluble compounds and by injections of calomel. Hydrargyrum salicylicum does not seem to be absolutely reliable, on the one hand because its chemical composition makes it decomposable only with difficulty, and on the other hand because of its extremely rapid elimination. The very common use of this remedy is probably due to the slight painfulness of the injections, but this advantage only justifies its use for exceptionally sensitive patients. Metallic mercury possesses the same advantage in a higher degree. But this remedy has a very serious drawback in its slow and sometimes very irregular absorption, which may in some cases produce severe intoxication, in other cases a feeble therapeutic effect. The treatment by inunctions possesses the advantage of being reliable, effective and painless, but unfortunately also dirty and tiresome for the patients. To obtain a rapid saturation of the body by mercury it may be of advantage to give at the beginning of the treatment an injection of a soluble salt of mercury, which is rapidly absorbed, or simply to give a dose of 0.5 gm. calomel per os. This produces the same effect. The daily dose of ointment to be used varies from 3 to 5 gm. according to the size, etc., of the patient. Children support well a comparatively large dose of this remedy. The treatment by injections of soluble compounds is not used very much nowadays, as the injections ought to be given with very frequent intervals (every day, or at least every second day). This makes the treatment rather complicated and wastes the patient's time. This treatment has a special indication in those cases of idiosyncrasia mercurialis, in which a tendency to "hydrargyria cutanea" prevents the use of inunctions. The treatment by injections of calomel has always been estimated to be of great therapeutic value. Still, the painfulness of the injections frequently met with prevents an extensive use of this very valuable remedy. The usual treatment by weekly injections of 8 to 10 cgrm. often causes considerable pain, but where the same dose is given in two injections every week and in an emulsion of 20 per cent, in the author's experience this treatment is supported well by most patients. In most cases 3 to 4 cgrm. per injection will do well and produce a valuable therapeutic effect. The best localization for the injections is, in the author's experience, an area a little below the iliac crest and rather to the side. To avoid intravenous injection of the emulsion it is advisable to wait a few moments after the insertion of the needle before the emulsion is injected. If blood exudes from the needle the injection should be made in another place.

**A Case of Jaundice From Late Salvarsan Poisoning.**—John Elliott, Chester, England. *Lancet*, London, 1921, vol. cc, p. 1180.

There can be no doubt that this was a case of late jaundice from salvarsan poisoning, the interval between the last injection and the onset of symptoms having been about 42 days. The symptoms are identical with those recently

recorded in similar cases by Major A. T. Todd. The author has seen no record, however, of a distended gall bladder such as existed in this case, his surmise that the distension was caused by effused blood, with blocking of the cystic duct by clot, being probably correct. Had he carried out his original intention of commencing the treatment with adrenalin and calcium the alarming collapse of the evening of Jan. 24th would almost certainly have been avoided. The hemorrhagic symptoms showed that the effect of arsenic on the capillaries, and probably also on the blood, had been reinforced by the dilution of the blood with the normal saline injected. His confidence that administration of adrenalin and calcium would render the subsequent intravenous use of saline a safe procedure was abundantly justified by the further course of the case. The diuretic effect of the saline was very evident, and there can be no doubt that it assisted materially in the elimination of the poisonous toxins. A marked feature of the case was the reaction which followed each injection of salvarsan, and the feeling of malaise and illness which induced us to intermit the treatment from time to time, and, fortunately, to discontinue it between Nov. 27th and the onset of the acute illness in January.

**The Toxicity and Trypanocidal Activity of Sodium Arsphenamin.**—Jay Frank Schamberg, John A. Kolmer and George W. Raiziss, Philadelphia. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1823.

The highest tolerated dose of sodium arsphenamine for white rats by intravenous injection was found to be from 212 to 215 mg. per kilogram of weight. The average tolerated dose of arsphenamine was 105 mg., and of neoarsphenamine, 200 mg. per kilogram. The smallest trypanocidal doses of sodium arsphenamine varied from 16 to 24 mg. per kilogram of weight; the smallest trypanocidal dose of arsphenamine was 5 mg., and of neoarsphenamine, 9 mg. per kilogram. The therapeutic dose (*dosis curativa*) of sodium arsphenamine was from eight to thirteen times less than the highest tolerated dose (*dosis tolerata*) which expresses the therapeutic index of this compound. The therapeutic dose of arsphenamine was twenty-one times less than the tolerated dose, and the therapeutic dose of neoarsphenamine was twenty-two times less. Therefore, while sodium arsphenamine possesses the low toxicity of neoarsphenamine, it is much inferior to both arsphenamine and neoarsphenamine in trypanocidal or curative activity. The true gage of a remedy is expressed by its chemotherapeutic index, i.e., the relation of the curative to the toxic doses.

**The Preparation of Colloidal Gold Solution for Testing Spinal Fluid.**—Alexander O. Gettler and J. W. Jackson, New York. *Archives of Neurology and Psychiatry*, 1921, vol. vi, p. 70.

Into a clean 1.5 liter Florence flask place 1 liter of water, distilled as outlined in the paper. To this add 10 c.c. of 1 per cent gold chlorid solution, 7 c.c. of 2 per cent potassium carbonate and 0.5 c.c. of 1 per cent oxalic acid. Heat this mixture to the boiling point, and at this temperature remove the



flask from the flame, holding it by means of a towel and shake vigorously. While the solution is still in motion, add quickly from 0.2 to 0.3 c.c. or ordinary concentrated 40 per cent chemically pure formaldehyde and at once shake thoroughly for from one-half to one minute. After from three to four minutes the color usually commences to develop. If, however, there should be no indication of color, the solution must again be shaken well and, while still in motion, an additional 0.1 to 0.2 c.c. of formaldehyde quickly added; this addition almost invariably produces the desired change. At no time during this process should the shaking be stopped. The color should develop rapidly to a deep red. If, however, there is a delay in the appearance of color, the mixture should be allowed to stand, and in a minute or two the color will start to develop; at this instant the solution should again be thoroughly shaken until the color reaches a deep red shade. The entire process, from the moment the solution reaches the boiling point until the color is fully developed, requires at the most about three minutes.

**Effect of Intravenous Administration of Arsphenamin, Neoarsphenamin and Mercury.**—Robert A. Kilduffe, Pittsburgh. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1489.

The drugs were given at weekly intervals, blood for the Wassermann test being withdrawn just prior to each injection, thus being taken one week after the preceding dose of each drug. The conditions, therefore, closely approximated those in the investigations of Strickler, Munson and Sidlick except that rabbits were used, thus excluding the possibility of syphilis and a provocative reaction. The Wassermann reactions were performed by Kolmer's second method, using three antigens: cholesterinized extract of human heart, acetone insoluble lipoids of human heart, and an alcoholic extract of syphilitic liver. The results were uniformly negative, a positive Wassermann reaction not being produced in any animal of any series. While these animals received less than the number of injections in Kolmer's series (from 6 to 10), and while it is conceivable that the effect of arsphenamine, neoarsphenamine and mercury on the qualities of human serums may vary from that produced in the serum of the normal adult rabbit, these results are, nevertheless, believed to be of significance and to indicate the necessity for further and extensive investigations of this subject.

**Clinical Commentary on Studies of Histologic Changes in Organs Induced by Arsphenamine, by Neoarsphenamine and by Mercury.**—Jay Frank Schamberg, Philadelphia. *Archives of Dermatology and Syphilology*, 1921, vol. iii, p. 571.

Both the arsphenamines and mercury administered in therapeutic doses bring about some structural alterations in organs. These are doubtless ordinarily repaired like the changes that take place in various acute infectious diseases. The chief organs affected by the arsphenamines are the liver, the suprarenals and the blood vessels. The effects of mercury, on the other hand, are seen dominantly in the kidneys and in the brain. The pathologic findings and clinical

experience would alike persuade one to utter two cautions: In mercurial treatment watch the kidneys; in arsphenamine treatment watch the liver. To be sure, as stated by Milian, in early syphilis jaundice may indicate either hepatic syphilis or a Herxheimer reaction, and will respond to more vigorous treatment when the less intense treatment has failed. Later in the disease, however, and particularly after the vigorous use of the arsenicals, the development of jaundice should lead to a suspension of all specific treatment. The treatment of syphilis requires the repeated use of these drugs. When used with circumspection and good judgment harmful results may in large part be avoided. When used unskillfully, without proper examination of the patient and without knowledge of warning signals, unfortunate results may take place. The fact should be emphasized that the body tolerates much larger amounts of arsphenamine than mercury. One may, for instance, administer intravenously to a white rat, fifty times as much arsphenamine as mercury. More mercury cannot be administered because it has too great an affinity for body cells. The therapeutic dose of arsphenamine is infinitely more destructive to the spirochete of syphilis than the therapeutic dose of mercury. The spirochetes in a chancre can be destroyed in a few hours by an injection of arsphenamine; this accomplishment is impossible with a single injection of mercury. Fatalities have occurred both after arsphenamine and mercury. Those after the former are much more tragic and fear-inspiring, for the relation between cause and effect is obvious. Many scores, if not hundreds, of deaths after mercury have likewise been reported in the literature, but they are ordinarily more apt to be slow and insidious and less likely to be incriminative of the therapeutic procedure employed. In conclusion, the writer cannot refrain from expressing his opinion that vigorous mercurial treatment is often responsible for arsenical intoxication when arsphenamine and mercury are used at the same time. Large doses of both ought not to be employed synchronously. When the two are used jointly their respective dosages should be inversely proportional to each other. It would appear best to give the courses of mercury subsequent to that of arsenic.

#### **Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis.**

—Joseph Earle Moore and Albert Keidel, Baltimore. *Archives of Internal Medicine*, 1921, vol. xxvii, p. 716.

The authors have presented a study of twenty-three cases of dermatitis and allied reactions following the use of arsenical products in the treatment of syphilis. Such reactions are equally frequent in either sex, but they are about three times as liable to occur in the white race as in the colored. Evidence is presented that the lesions of syphilis or the duration of the disease exercise no modifying influence upon the incidence of dermatitis. Two of their twenty-three cases occurred in patients in whom syphilis could be ruled out. Dermatitis has been observed to follow all chemotherapeutic arsenic compounds which we have employed in the treatment of syphilis. In the majority of cases in this series, arsenic was the only drug employed so that mercury and potassium iodide as causative factors can be excluded. Reactions of this group tend to appear early in the course of treatment. In some cases,

certain prodromal symptoms may be recognized. These consist of itching, mild or fleeting macular, maculopapular, or vesicular skin eruptions, stomatitis, prolonged fever, or marked malaise. The occurrence of any of these during the use of arsenical products should lead to a suspension of treatment and a general survey of the patient. Dosage, technic of administration, and impurities in the drug can be excluded as etiologic factors. The lesions may be classified, on the basis of the constitutional manifestations and their importance, as mild or severe. In the mild group fall urticarial, erythematous and herpetic rashes. In the severe group are the macular, maculopapular, and exfoliative rashes, itching and stomatitis. Urticaria is fairly common in association with the nitritoid crisis. The more severe constitutional manifestations are absent, and in most cases arsenical treatment may be continued. No patient so treated has later developed a more serious rash. The same may be said of herpes simplex and the erythematous rashes, except that in these cases fever and leucocytosis are frequently found. The characteristics of the rashes of the severe group are described. Attention is drawn to characteristic alterations in the blood picture, which were present in fourteen of sixteen cases studied. The changes consist in general of leukopenia, decrease in polymorphonuclear neutrophils, eosinophilia, increase of the large mononuclear transitional group, and the appearance of many fragile cells. The complications of dermatitis exfoliativa, including acute nephritis, polyneuritis, jaundice, skin infection, bronchopneumonia, and septicemia, are discussed. Attention is directed to the possible relation between the complications due to infection and the disturbance of hematopoiesis. The sensitiveness of the patient to the drug causing the original reaction persists over long periods of time and is made manifest by even small doses of the same drug. However, certain patients, who cannot be accurately distinguished, are able to take other less toxic arsenical drugs without the development of reactions of this type. The prognosis of these reactions is grave. Among our series of twenty-three patients there have been five deaths. The pathologic picture is briefly described. Patients with itching without skin lesions, and with stomatitis due to arsenical preparations have been found to present a blood picture similar to that described in the exfoliative dermatitis group. The literature is reviewed, and the possible etiologic factors in reactions of this group are discussed. The evidence is in favor of their anaphylactic origin.

**Arsphenamine Dermatitis.**—George Manghill Olson, Minneapolis. *Journal-Lancet*, 1920, vol. xl, p. 338.

Arsphenamine dermatitis is a not uncommon affection of the skin at the present time, due to the more general use of arsphenamine, and the increased total dose that patients now receive. The clinical picture of arsphenamine eruptions is varied and extremely complex. The rash may be delayed for weeks or months after the injections of arsphenamine have been discontinued. Arsphenamine eruptions are nearly always due to the direct inflammatory action of arsphenamine on the various elements of the skin. The toxicity of arsphenamine, as shown by acute accidents as sudden collapse and death, and remote accidents as derma-



titis, is inherent in the substance itself. The inherent toxicity of arsphenamine is greatly increased by poor manufacture or imperfect technic in its administration. To patients in whom there occurs a storage or retention of arsphenamine, further injections must be given with caution, as serious or even fatal results may follow. Treatment is symptomatic. Venesection is of value in the acute forms of arsphenamine eruptions. Improvement in the chronic or subacute forms of arsphenamine dermatitis follows the use of actinic or ultraviolet light and the x-ray.

**Nerve Injuries Due to Errors in Technic in Making Intravenous Arsphenamin Injections.**—Dean Lewis, Chicago. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 1726.

Two examples of nerve injury caused by errors of technic in making arsphenamine injections are reported to emphasize the need of extreme care. Pain radiating into the fingers when the first few drops of the solution are injected should be a warning that the needle is not in the vein and that the solution is being injected directly into a nerve or into the tissue surrounding it. Arsphenamine injected into or about a nerve may have a marked destructive action, causing extensive degeneration of neuraxes and the development of large amounts of scar tissue. The densely adherent scar which follows sloughing of the skin, if such occurs, may seriously interfere with or render unsatisfactory a nerve suture.

**Treating Syphilitics.**—Leo L. Michel and Herman Goodman, New York City. *New York Medical Journal*, July 20, 1921.

These authors summarize their paper as follows:

The patient with syphilis, and not syphilis should be considered by the physician when it comes to treatment. The tissues of the patient are worthy of respect, especially when one considers that the assault of the drugs needed in treatment is added to the tissue damage of the spirochetes.

Specific treatment of the syphilitic requires arsphenamine, or one of its newer salts, neoarsphenamine, sodium arsphenamine, or silver arsphenamine. Mercury is also used in the specific treatment. The iodides are very valuable, especially in the later stages of the disease.

The use of arsphenamine in the prophylaxis of syphilis is a phase in treatment that is very important, and its results make it worthy of wider use. Its share in the public health aspects of this disease are especially valuable.

The intensive treatment in the early syphilitic, both when the abortive action and the quick and thorough sterilization of the patient seems feasible, is recommended for otherwise healthy persons with syphilis. Care in selection of the patient for this form of therapy is of first importance.

Modified forms of injection of arsphenamine should be given according to the patient, the reactions of his excretory organs, response to drugs, and phase of the disease process.

Iodides form a valuable addition, and the intravenous route should be considered, especially if large doses by mouth tend to upset the patient.

Systematic and systemic examination of the patient should be made at intervals, with especial reference to the cerebrospinal system. When indicated, the lumbar puncture for diagnosis and treatment is advised.

Routine treatments in syphilis should be disregarded. Every syphilitic patient should be treated as an individual requiring attention, and not as a case of syphilis.

**The Treatment of Cases of Syphilis Having a Persistent Positive Wassermann Reaction.**—C. F. Marshall and A. G. Shera, Eastbourne, England. *Lancet*, London, 1921, vol. cc, p. 1299.

The authors are of opinion that the possibility of the Wassermann reaction remaining positive in the absence of active spirochetosis has not yet been disproved. But as it is equally impossible to disprove the contrary hypothesis, it is best in actual practice to regard a patient with a persistent positive reaction as one who is not definitely cured and as a subject for further observation and possibly further treatment. They consider that a persistent positive reaction is not, by itself, sufficient evidence to decide the question of further treatment, and that we should be guided equally by the clinical progress of the case, the nature of the former symptoms, and the intensity and duration of previous treatment. If clinical symptoms have been present comparatively recently (say, during the last 12 months), they hold that further treatment is advisable; but if symptoms have been absent for more than a year, that the advisability or not of further treatment should depend chiefly upon the clinical course of the case. If further treatment is decided upon they think that this should differ materially from that given previously. They suggest that sulphur should form part of this treatment without venturing on any hypothesis to explain its possible action.

**Cacodylate of Sodium and the Painful Crises of Tabes.** Maréchal (Paris). *Gazette des Hôpitaux*, February 19, 1921, xciv, 15.

In 1918 the author, having made a comparative study of the therapeutic activity of salvarsan and sodium cacodylate, announced that the field for the latter is much wider than has been conceded by the Americans. He recommended that the salt be injected in a fifty per cent solution directly into the veins. Since that period his suggestions have been widely followed in France and the two methylarsinates—cacodylate and arrhenal—now have an extensive following. In fact organic arsenic in large doses has been used to fill many of the old indications for the element, such as chronic eczema. It occurred to the author to test the cacodylate in the painful crises of tabes and he has had this opportunity in 5 cases. The condition is notably difficult to influence by treatment and he was not optimistic over the outlook. One of the more favorable cases was as follows: male, age 50, typical tabes, painful seizures began in 1908, treated with calomel injections in 1913 and during 1914 received 140 of biniodide, with no arrest of pains. In 1915 six courses of grey oil injections. No mention

of 1916. In 1917 several courses of cyanate injections and in 1918 numerous injections of benzoate. The pains could not be controlled. Had *malum perforans pedis* and bilateral Charcot joints, the former ending in 1919 in a Chopart amputation. During December, 1919, he received a course of cacodylate injections with some benefit. The treatment continued during the winter and by April 1 he was free for the first time. In October reappearance of vague pains which yielded to aspirin. In this case after more than 10 years of almost continuous suffering the patient was made comfortable by the cacodylate injection.

**Treatment of the Pregnant Syphilitic Woman.** Mareel Pinard (Paris). *Journal de médecine et de chirurgie pratiques*, February 10, 1921, cviii, 3.

The author introduces the subject of infected semen and the possibility of intrauterine and intraperitoneal contamination and of infection of the fertilized ovum. In the latter eventuality we would expect a placental infection of the mother. Whatever the mechanism of this seminal infection there would be no tell-tale chancre or any secondary outbreak that may be detected. The woman will give a positive seroreaction but while the child may show every form of congenital syphilis including miscarriage the disease in the mother remains as far as known latent. The condition is radically different from that seen in the gravida who is infected in the usual manner and who develops primary and secondary manifestations. It is admitted that this conceptional syphilis, long accepted by former clinicians, has been denied outright by Carle and others, so that to a certain extent we speak of it hypothetically. In a suspicious case we must examine and follow up with extreme care both father and mother. The seroreaction should be checked up by some other method than the one first used and repeated tests made. A negative outcome may mean nothing. The obstetrical history of the mother must be carefully obtained for the infection may have occurred at an anterior gestation. There should be a provocative injection of arsenic and a lumbar puncture. In case of a positive reaction we should treat the woman intensively in the interest of the fetus. The author likes the intramuscular method best with neosalvarsan in a glucose solution and also recommends hypodermics of sulpharsenol in distilled water.

**Relative Effectiveness of Various Forms of Treatment in Neurosyphilis.**—John H. Stokes and Earl D. Osborne, Rochester, Minn. *Journal of the American Medical Association*, 1921, vol. lxxvi, p. 708.

A comparison of the findings on patients receiving spinal drainage in conjunction with arsphenamine intravenously and routine mercurialization, and the findings on patients receiving an equal amount of routine treatment without spinal drainage, demonstrates no superiority in favor of the drainage method. The most immediate change produced by either of these methods of treatment is in the cell count. A transient but marked rise followed by a fall toward normal limits occurred in patients receiving spinal drainage, and the authors have reason to believe that a similar Herxheimer-like curve of pleocytosis accompanied by



transient exacerbation of symptoms occurs in many patients under treatment for neurosyphilis by routine methods. Temporary rise in the cell count early in the course of treatment should not therefore necessarily be regarded as of unfavorable prognostic significance. In ten patients in whom spinal drainage had produced indifferent results, the administration of arsphenamine serum intraspinally some months later produced what appeared to be more satisfactory and more permanent results.

**Is It Necessary to Treat the Pregnant Wife of a Syphilitic?** Carle (Lyon). *Annales de dermatologie et de syphiligraphie*, January, 1921, vi series, ii, 1.

The author is convinced that paternal syphilis is innocuous and that it is not necessary that every wife of a syphilitic be submitted to routine treatment. This view is of course not held by the majority of practitioners, who would at least give the women ordinary treatment by the mouth as a precaution. Naturally an intensive cure might gain the reputation of having jugulated something that never really existed. The author refers only to conceptional infection. If the woman has been infected by the husband by any of the usual methods she must of course be treated like any other recent syphilitic. In past decades Fournier, Finger and the late Gaucher all believed in the routine treatment of any wife of a syphilitic, with special reference to pregnancy in the interest of the unborn. But this was in 1900 and 1900 is not 1920. Apparently Gaucher changed his views, for he accepted the presidency of Bobret's thesis in 1912, and Bobret is one of the few who uphold the author's position.

Back in 1899 the author used to treat all pregnant wives of syphilitics surreptitiously as it were without letting them into the secret. He gave them disguised pills and syrups. This worked out poorly in several ways. The treatment was not intensive enough to prevent miscarriage in the frankly syphilitic while some women who knew the author's aim believed themselves immune, as a result of treatment when they were infected. After the Wassermann came into use he declined to treat the pregnant wives of syphilitics unless convinced of their infection—in which case there would be the justification of intensive prolonged treatment; if the woman seemed intact he had the courage of his convictions and refused to treat her.

**The Modern Treatment of Syphilis of the Central Nervous System.**—H. G. Mehrtens, San Francisco. *California State Journal of Medicine*, 1920, vol. xviii, p. 385.

Our present methods of treating neurosyphilis are by no means so successful as we would like to make them. Certainly the last word has yet to be said, particularly in the development of the intradural methods. Even so, we can feel that our present methods enable us to arrest cases intractable to the older methods and give us hope that the future will evolve methods which, used in time, will arrest a large majority of cases of neurosyphilis.

**The Treatment of Neurosyphilis by the Intrapinal Route.**—Albert Keidel and Joseph Earle Moore, Baltimore, Md. *Bulletin of the Johns Hopkins Hospital*, 1920, vol. xxxi, p. 404.

Intrapinal therapy is a necessary and rational adjunct in the treatment of neurosyphilis in cases which fail to respond to routine antisyphilitic treatment. The mode of action of intraspinal medication does not depend upon increased permeability of the meninges. Aseptic meningitis produced by intraspinal injection of irritants may prove an untoward rather than a beneficial factor in the treatment of neurosyphilis.

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